

ANNUAL REPORT OF THE INTRAMURAL RESEARCH PROGRAM

Office of the Scientific Director	IRP-OSD-1
Research Resources Branch	IRP-RRB-12
Longitudinal Studies Branch	IRP-LSB-17
Laboratory of Behavioral Sciences	IRP-LBS-55
Laboratory of Biological Chemistry	IRP-LBC-96
Laboratory of Cardiovascular Science	IRP-LCS-126
Laboratory of Cellular and Molecular Biology	IRP-LCMB-201
Laboratory of Clinical Physiology	IRP-LCP-245
Laboratory of Molecular Genetics	IRP-LMG-341
Laboratory of Neurosciences	IRP-LN-372
Laboratory of Personality and Cognition	IRP-LPC-514

PC

952

N277

1986

pt. A

ANNUAL REPORT OF THE OFFICE OF THE SCIENTIFIC DIRECTOR

NATIONAL INSTITUTE ON AGING

The Scientific Director, NIA, is responsible for the quality and direction of research undertaken by the intramural program. In addition, the Office of the Scientific Director embraces selected administration, information, and support functions essential to the program's efficient operation.

The structure of the OSD was altered significantly under the recent reorganization and the purposes underlying the changes affecting OSD seem to have been met this year: Reducing the number of functions and personnel assigned to the Scientific Director's immediate office, thereby ensuring a more appropriate span of control; promoting increased efficiency and responsiveness in the provision of services to intramural investigators; and, providing an operating structure which is both logically and functionally more coherent.

The organizational units which comprise the reconstituted OSD are Administrative Services, which includes the Administrative Office and Procurement; the Information Office and the intramural Personnel Office. The achievements of these units are highlighted on subsequent pages as is the progress of one research project conducted under OSD auspices.

Among the activities and developments which warrant special mention here with regard to the total intramural research program are the following:

Longitudinal Studies Branch. This new branch and its leader have made an extremely impressive beginning in resolving many of the complex issues inherent in the Baltimore Longitudinal Study of Aging (BLSA) enterprise. The upcoming review by the Board of Scientific Counselors (October 1986) should be invaluable in eliciting advice on how to make further improvements in the operation of the BLSA and in charting the future of this study.

Geriatric Inpatient Continence Research Program. One of the collaborative ventures highlighted in last year's report, this program is proceeding well. Supported in part by the Health Care Financing Administration, this effort is now a going concern and is discussed in greater detail in the Laboratory of Behavioral Sciences report.

General Clinical Research Center. The inpatient unit of this joint NIA/Francis Scott Key Medical Center GCRC begins operations in November of this year. The advent of this clinical facility will enable NIA intramural investigators to engage in a variety of on site research studies involving the ailing elderly and should further enhance the utility of the highly characterized BLSA population.

Productivity and Recognition. Even with the budgetary cutbacks and less staff, the IRP component has remained productive. This is evidenced by the publication of 253 papers, chapters or other manuscripts between January 1, 1985 and June 30, 1986. In addition, staff dedication and skill is evidenced by the happy fact that some 60 IRP workers received group or individual performance awards this year.

Administrative Services

Administrative Office. This office provides a wide range of support services essential to the effective operation of the Intramural Research Program. The nature and extent of the administrative function differs significantly from that of other Institutes due to the distance to the NIH complex and the requirement to operate and maintain a separate facility.

AO responsibilities encompass budget management, station support, contract monitoring and administration, building operations, travel review and authorization, property accountability, administrative reporting, personnel ceilings, timekeeping, and payroll disbursing, space, telephone service, and safety. The Administrative Officer also participates in many of the intramural committees which play an instrumental role in the governance of the IRP.

The following describes Fiscal Year 1986 office activities.

- o Budget Management. Overseeing the IRP budget is ongoing and includes the recording of daily procurement obligations for each section and branch and monitoring spending levels to assure areas remain within allocated funds. To provide section and branch chiefs with the means for planning program expenditures, the weekly and monthly NIH accounting reports are verified against in-house records to assure accuracy.
- o Contract Monitoring and Administration. The Administrative Office is responsible for a number of contracts providing building services such as housekeeping, security, building maintenance, utilities, waste disposal, and radiation control. These responsibilities range from the initial preparation of a Statement of Work to the evaluation of the contractor's performance. Services provided by the contracts are essential to the operation of the GRC facility and require daily monitoring by the AO and close interaction with contract staff.
- o Property Accountability. This year the reorganization and a reallocation of space resulted in an increased workload. Additional custodial codes were established to cover the newly formed branches. This necessitated numerous property transfers from one custodial code to another. This project will be completed early in FY 1987 and when finished will provide us with an up-to-date accountability system.
- o Personnel Ceiling. The AO continues to monitor FTE usage and prepare reports for use by the Scientific Director and the NIA Budget Office. These reports help plan staffing and recruitment actions in addition to presenting the status of the FTE plan.

The Administrative Officer continues to review requests for personnel actions before submission to the Scientific Director. After his approval personnel actions are initiated by this office.

Procurement/Receiving Unit. The Procurement and Receiving Unit is responsible for the direct purchase and receipt of all procurement goods within the delegated authority of \$2,500. They also monitor all requisitions sent to the NIH Central Procurement for the GRC.

Gerontology Research Center procurement actions processed from August 1985 through July 1986 were as follows:

SF-147 (Purchase Order)	1,267
TCO	59
Record of Calls	2,516
Reprint Orders	77
NIH-402 and On-Line Market Requisitions	226
Repair Orders	64
SF-44 (Petty Cash Vouchers)	366
Stock Requisitions	1,016

Information Services

IRP Information Office. During FY 1986, the IO expended much of its time working on several special projects, enhancing programs for employees, working with the media, and writing articles and other material for publication in professional or government publications to stimulate interest in research underway at the NIA.

In the late summer and fall, IO staff worked closely with the Laboratory of Behavioral Sciences helping them plan, organize and dedicate the the Inpatient Geriatric Continence Unit, co-sponsored by NIA and HCFA at the Francis Scott Key Medical Center (FSKMC). Staff helped develop the overall guest list, handled invitation logistics, did all the publicity for the opening, and held a press briefing. The latter resulted in stories over Baltimore Channels 2 and 13, in THE BALTIMORE SUN and BALTIMORE CHRONICLE. Later publicity appeared in the APA MONITOR, INTERNATIONAL MEDICAL NEWS, and THE NIH RECORD, THE BANNER (FSKMC employee newsletter), and FSK's magazine, KEYNOTES.

Efforts of the Information Office in publicizing the book, Normal Human Aging, and sending copies to editors resulted in excellent reviews overall in JAMA, CONTEMPORARY PSYCHOLOGY, GERONTOLOGY, JOURNAL OF GERONTOLOGY, EXPERIMENTAL GERONTOLOGY, and EDUCATIONAL GERONTOLOGY.

Related to Normal Human Aging, the IO prepared a concept clearance document to prepare and publish a less technical version of the book for nonscientists, tentatively titled "A Lifetime of Aging." The clearance proved complicated and required considerable additional justification before departmental approval was finally given.

At the request of Dr. Bernard T. Engel, another project this year was the operation of a press desk, for the first time, at the annual meeting of the American Psychosomatic Society. The IRP Communications Officer (CO) prepared a media alert and manned the press desk during the meeting held in Baltimore, supplying material to several media contacts before, during and after the meeting. The CO also served as an assistant press officer at the New Orleans Gerontological Society of America meeting, helping to publicize work done by both intramural and extramural grantees.

Other important projects of the office this past year included organizing two very successful blood drives in December and June (123 units donated via both drives), and two well-received IRP employee award ceremonies.

The office carried out a number of writing assignments. Two articles were written for NEWS AND FEATURES FROM NIH--one on biofeedback treatment of incontinence; the other on exercise benefits in late life. An article on Dr. Josef Pitha's work relating to the effectiveness of oral steroid hormones was written for a future "From the NIH" column in JAMA. A paper by a former NIA employee on the early years of GRC was written with the help of this office and will appear in a special December two volume issue of EXPERIMENTAL GERONTOLOGY. The reorganization of the IRP led to the extensive revision of the Institute's submissions for the NIH Medical Staff Fellow and Summer Research Fellow catalogs. In addition, material describing the new organization was compiled and submitted for a number of independently produced directories.

A description of the newly established Laboratory of Personality and Cognition was prepared at the request of the APA MONITOR. In addition, five stories were written for THE NIH RECORD; several for newsletters published by NIH components or special interest groups. The office also edited and provided suggestions for the NIA Biennial Report and a manuscript by the Scientist Emeritus to be published in SCIENTIFIC AMERICAN. The IO's editorial assistant provided assistance to the staff of various laboratories in the preparation of scientific manuscripts and assisted in the editing and processing of an historical manuscript concerning the International Association of Gerontology.

Direct contact with the public is another important function of this office. This year, over 700 people from scientists to high school students were briefed via tours and speaking engagements. Special programs were arranged for graduate students from the University of Maryland Center on Aging, UM Medical School, Human Factors Society (2), an honorary psychology student group, Maryland Junior Science Symposium attendees, and visitors from Cuba, Italy, Japan, and Thailand.

Interaction with the media is an important part of IO activities every year. In FY 1986, the office worked with CBS-TV Morning and Evening News on stories aired last fall and with WMAR-TV (Baltimore) on a three-part series which earned the reporter a special award from the Maryland Medical and Chirurgical Society. John Chancellor of NBC-TV News spoke extensively with the CO regarding age and the presidency as did a reporter from the WASHINGTON POST around the time of President Reagan's 75th birthday.

Major stories on aging appeared in LADIES HOME JOURNAL, SKY (Delta Airlines), REDBOOK, THE TIMES-UNION (Rochester, N.Y.), and PSYCHOLOGY TODAY. Most impressive was the five page article on aging and the NIA which appeared in JAMA (Feb. 21, 1986). The office also worked with reporters, arranging numerous interviews, for an upcoming series this fall in THE PROVIDENCE (R.I.) JOURNAL and a major feature in TIME. Overseas cooperation has included that with Australian Broadcasting, KOREA TIMES, LONDON DAILY MAIL, English television, and INTERNATIONAL MAGAZINE (Saudi Arabia). In addition worked with USIA's TOPIC MAGAZINE and CBC Radio and Television.

Closer to home, the IO prepared 12 issues of the internal newsletter, GERON NEWS and two issues of SIX S's NEWS (an information packet for Baltimore Longitudinal Study of Aging participants. Finally, a number of cultural or educational programs for NIA staff were coordinated by the staff, including film showings or presentations on tax preparation, self-monitoring of glucose, strokes, vision loss, and the value of animals in research. Helped in planning and publicizing Employ the Handicapped Week, Black History Month, seminars, or other events at the Baltimore unit.

The Communications Officer was honored with an award from the NIH Division of Equal Opportunity for his work as chairman and as a member of the Handicapped Employees Committee and, this summer became third vice president for off-campus activities of the Recreation and Welfare Association.

Highlights of IRP information activities for Fiscal 1986 follow.

Special Projects

- o IO helped plan, provided logistics support and publicized opening of Geriatric Inpatient Continence Unit.
- o Prepared concept clearance and provided extensive justification for popularized version of Normal Human Aging.
- o Helped publicize and manned press room for annual meeting of the American Psychosomatic Society.
- o Chaired and organized two productive blood drives at the GRC.
- o Planned and carried out logistics for two well-received IRP employee recognition ceremonies.
- o Helped publicize successful 1986 U.S. Savings Bond Drive.
- o Coordinated IRP annual report, supplying editorial and other services as needed. Compiled and edited mid-year and annual bibliography and directory submissions.
- o Did a thorough job of updating IRP Staff Profiles, including taking new staff photographs as needed.

Articles/Publications/Editorial

- o Wrote NIH RECORD story with photographs on opening of the Geriatric Inpatient Continence Unit. Another story on biofeedback treatment published in NEWS AND FEATURES FROM NIH.
- o Helped write and edit article by retired GRC employee for upcoming EXPERIMENTAL GERONTOLOGY publication.
- o At request of APA Monitor, prepared description of newly established Laboratory of Personality and Cognition for that publication.
- o Article on effectiveness of oral steroids, based on Dr. Pitha's studies, written for JAMA "From the NIH" column.
- o Story on lecture by Dr. Andrew Goldberg concerning exercise benefits published in July 1986 NEWS AND FEATURES.
- o Five articles prepared for NIH RECORD, including story on appointment of Dr. James Fozard as Associate Scientific Director for the BLSA.
- o Staff provided editorial assistance to several IRP laboratories in preparing research manuscripts and to the NIH Scientist Emeritus for a number of papers or articles.
- o Revised Medical Staff Fellow and Summer Research Fellow catalogs extensively to reflect IRP reorganization.
- o Provided newly written descriptions of IRP programs for a number of research directories or catalogs.
- o Wrote media alerts or press summaries, backgrounders for continence unit opening, GSA meeting, American Psychosomatic Society meeting.

Newsletters

- o Wrote article on incontinence therapy for "Hot Flash" newsletter.
- o Did short items for Clinical Center CLOSEUP newsletter and for SHER group's newsletter in Bethesda.
- o Collected material, wrote, edited, and published 12 issues of NIA internal newsletter, GERON NEWS.
- o Published two very informative issues of SIX S's NEWS, an information letter provided to BLSA participants.

Media Interaction

- o Aided John Chancellor, NBC-TV News and THE WASHINGTON POST with stories on functional age and the presidency.
- o Provided considerable assistance to CBS-TV Morning and Evening News for mini series on aging, aired in September and November, 1985.
- o Arranged interviews with Dr. Richard Greulich and Dr. Reubin Andres for WBAL Radio and WBAL-TV programs.

- o Helped reporters with major stories on aging appearing in LADIES HOME JOURNAL, REDBOOK, YORK DAILY RECORD, ROCHESTER TIMES-UNION, and PSYCHOLOGY TODAY.
- o Provided extensive background and suggested interviews for five page article, featuring NIA, in JAMA issue of February 21, 1986.
- o Assisted international media, including Australian Radio, KOREA TIMES, LONDON DAILY MAIL, CBC Radio and Television, and a commercial British television station with stories.
- o Provided referrals and arranged IRP interviews for TIME in connection with upcoming fall 1986 feature article on aging.
- o Other major contacts this year were made with GENTLEMEN'S QUARTERLY, UPI; NATIONAL GEOGRAPHIC, U.S. NEWS AND WORLD REPORT, PROVIDENCE JOURNAL, WASHINGTON TIMES, WRC-TV, American Medical Radio News, INTERNATIONAL MEDICAL NEWS, MONEY MAGAZINE, and ESQUIRE.

Outreach Education

- o Briefed two groups (18) of St. Joseph's Hospital nursing students.
- o Spoke to Gaithersburg chapter of NARFE. Sixty-five members attended.
- o Gave guest lecture to 30 College of Notre Dame weekend students.
- o Featured lecturer for two biology classes at Dundalk (MD) High School.
- o Helped arrange program and participated in "Geriatric Imperatives" course offered by University of Maryland Medical School.
- o Set up program and laboratory sessions for 20 high school students attending annual Maryland Junior Science Symposium.
- o Addressed residents and staff of Charterhouse retirement facility in Silver Spring, Md.
- o Took part in planning, carrying out day-long session for members attending NCOA annual convention.
- o Held two special programs over two day period for members of Human Factors Society.
- o Toured/briefed visitors from Cuba, Italy, Japan, and Thailand.

Other Activities/Training

- o Communications Officer participated in 1985 National Association of Government Communicators annual conference and 1986 Region 2 meeting of the Society of Professional Journalists.

- o Jan Ehrman and Dan Rogers took part in fall educational seminar of Maryland Hospital Public Relations Society.
- o CO received NIH DEO recognition award for handicapped committee work.

Information Activities Summary
October 1, 1985-September 30, 1986

*SPECIAL PROJECTS.....	18
**ARTICLES/BACKGROUNDERS/PAPERS/PRESS NOTICES.....	21
SPEAKING ENGAGEMENTS/BRIEFINGS/TOURS.....	40
PEOPLE ADDRESSED.....	705
MEDIA INQUIRIES (U.S.).....	175
MEDIA (INTERNATIONAL).....	10
REPORTS.....	2
EMPLOYEE EDUCATION PROGRAMS.....	11
AUDIO/VIDEO TAPINGS.....	32
OUTREACH EDUCATION FILM/SLIDE LOANS.....	4
***INTERNAL NEWSLETTERS.....	14
PUBLIC INQUIRIES (MAIL AND PHONE).....	400
PUBLICATIONS/ARTICLES/REPRINTS DISTRIBUTED.....	4925
* Includes planning, logistics, press briefing for continence unit opening; 2 blood drives; publicity for bond drive; 2 employee awards programs, annual report and annual bibliography coordination; running publicity program for American Psychosomatic Society, etc.	
** Encompasses 1 article for JAMA; 1 paper for EXPERIMENTAL GERONTOLOGY; 2 for NIH NEWS and FEATURES; 5 for NIH RECORD; 1 for HOT FLASH, etc.	
*** Includes 12 issues of GERON NEWS and 2 SIX S's NEWS (BLSA).	

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00101-10 OSD

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Relation Between Nutritional State and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.H. Barrows, Jr., Chief, Section on Comparative Nutrition

OSD, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Gerontology Research Center, Office of the Scientific Director

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

1.0

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

1. Feeding enriched diets, i.e., those high in vitamins, minerals and fat to 23-month old male mice failed to defer the loss of body weight associated with senescence, and shortened the remaining life span by 20%.

2. Diets containing 50% cellulose markedly increased the life span of mice whereas those containing 33% cellulose were only minimally beneficial. This is the result of an apparent adequate compensatory increased food intake by animals fed the latter diet. The cellular protein synthesis of the liver of animals fed both levels of cellulose were reduced approximately 30%.

3. Continued studies confirm earlier observations that the life span of genetically determined diabetic mice is markedly increased by feeding an adequate diet intermittently, or a diet low in protein. In addition, although the addition of 50% cellulose to an adequate diet did not increase the life span of diabetic mice, reducing the cellulose to 33% of the diet was the most effective dietary manipulation to increase the life span of these animals.

IRP-OSD-9

ANNUAL REPORT OF THE RESEARCH RESOURCES BRANCH

NATIONAL INSTITUTE ON AGING

The newly established Research Resources Branch (RRB) consolidates major elements of research resources and technical support services. This branch is designed to promote increased efficiency and responsiveness in providing research resources and services to intramural investigators. The RRB is composed of the Technical Development Section, Photography and Arts Unit, Library Unit, Animal Resources Section, and the Instrument Design and Fabrication Section. The responsibilities and accomplishments of each of these components follows.

Technical Development Section

This section provides technical support to the GRC staff including the following: (1) operation and development of the GRC central computer system and consultation and assistance for its users; (2) supports the design, development and installation of small computer systems for specialized laboratory applications; (3) coordinates the facility's system and ADP policy with the NIH Division of Computer Research and Technology; and, (4) Maintains existing electronic equipment and devises new electronic instruments to meet the special needs of intramural staff.

Activities and Achievements

Over the past year, no major expenditures were made to expand the central VAX computer system due to budget constraints. However, the first step toward "clustering" our two CPUs was made with equipment purchased earlier. At the present time, all of our discs and printers are equally accessible for either of the two CPUs. This was a significant step toward a totally clustered configuration which allows the dynamic balancing of loads on the CPUs and allows for future efficient expansion.

A major development effort was made to integrate the various existing graphics devices into an "any-package-talks-to-any-device" environment. The reasoning supporting this major effort is as follows.

- o A major increase in the use of inexpensive graphics terminals by the labs, indicating a preference for the use of graphics as a part of their data reduction process.
- o The demonstrated willingness of many to reduce the burden on the Photo and Arts Unit by accomplishing part of the artwork themselves with easy-to-use system packages.
- o The increased efficiency of Photo and Arts which is already obvious.
- o The desirability of a posture where future procurement of high quality graphics devices, such as film recorders (color slide makers) and color printers, can be made without the usual limitations caused by existing software or having to purchase new software.

This effort entailed the creation of a set of common graphics primitives, the development of individual software drivers that use the primitives to control each device, the development of a graphics sub-routine library to generate the primitives, and the rewriting or modification of our existing software packages. This project is very near completion and will be released for general use when documentation is finished.

A second major effort by the TD section was to familiarize ourselves with the IBM PC in order to provide the staff with consultation and interfacing services. This current effort is covering many areas simultaneously:

- o Configuration of a laboratory-based PC as an Ethernet node of the central VAX computer, allowing extremely fast data transfer.
- o Familiarization with the hardware structure and operating system of the PC, which will allow the development of hardware interfaces unique to a particular application.
- o Evaluation of a Fortran compiler to determine its feasibility and limitations in the development of lab software.
- o Evaluation of other versions of Basic to determine their feasibility and limitations in the development of software.
- o Evaluation of terminal emulators that allow the PC to be used as a VAX terminal and one of the supported graphics devices.
- o Evaluation of commercial lab interface packages to discern their feasibility and limitations in the development of lab software.

Photography and Arts Unit

This unit provides a variety of art and photography services to GRC research staff. This includes: (1) a full range of art services, including publication design, poster design, statistical, technical, and scientific illustrations; (2) photographic services such as general and medical photography, photomacrography, patient photography, photographic copying, production of both black and white and color projection slides, slide duplicating, ekta-chrome transparency film developing, black and white developing, photographic printing, and overhead transparency production; and, (3) equips and services the audio-visual equipment located in the two conference rooms on the first floor of the GRC.

Activities and Achievements

In addition to the normal production of negatives, slides, prints, and poster materials, considerable development was devoted to integrating our graphics systems within the building and to making it independent of the graphics device in use. This integration will help investigators create their own graphics material on a variety of existing programs which can then be sent to this unit for modification as needed.

An increased demand for service this year and the loss of staff were partially offset by an increased use of the computer graphics system.

Time was saved by investigators generating their own graphics and because time expended using the computer is far less than that needed using conventional processes.

The unit recently purchased a Camag Reprostar/Transilluminator UV lightbox for photographing DNA gels prior to quenching. This ultraviolet lighting system delivers high quality photographs of thin layer chromatography plates and electrophoresis gels. Wave lengths of 254 nm, 300 nm, and 366 nm are possible, with either transmitted or reflected light. The unit has been set up and tested and can now provide these services to the building.

During the past year, the unit's color processing was moved to a new location on the second floor. New equipment has been installed and the new darkroom is ready for production. This should provide for a faster turnaround on color film development.

Library Unit

The Gerontology Research Center Library serves as a resource center, disseminating information in book and journal formats to support intramural and extramural investigators engaging in various disciplines related to aging research.

Activities and Achievements

- o The Librarian has performed some 200 computerized literature searches for intramural scientists.
- o A new database vendor, DIALOG, was set up through an interagency agreement with FEDLINK. It has allowed the Librarian to search some major chemical databases that are unavailable on BRS and NIM (the two other database vendors currently in use). The total budget for searches was not increased, but the same amount was redistributed among the three vendors.
- o A wide range of intramural research interests have been satisfactorily supported by the interlibrary loan service. Over the past 12 months, 988 photocopied articles and 52 books were acquired from other libraries. Approximately two-thirds of these were provided free of charge by the NIH Library and the National Library of Medicine. The other one-third were acquired with fees paid from other universities or research libraries.
- o A thorough inventory inventory was performed with these results:

1. Library Holdings:

a. Total Number of Books	7,450 volumes
Regular books	3,300 volumes
"Aging" books	3,200 volumes
Reference books	710 volumes
Aging/Reference books	90 volumes
Reports	150 volumes

b. Total Number of Journals Owned	700 titles
Number of Current Subscriptions	491 titles

c. Total Number of Bound Journals	8,900 volumes
Total Number of Unbound Journals	16,000 issues

2. Laboratories' Permanent Loan Books	1,500 volumes
---------------------------------------	---------------

- o A special effort was made in collection development to enrich our gerontology/geriatrics and reference book holdings. Three hundred and fifty new books were purchased for the Library and an additional 180 books for the intramural laboratories. All of these books were cataloged by the Librarian using the OCLC online cataloging system. The Library maintains a centralized file for GRC's entire book collection.
- o Despite the extreme manpower shortage, Phase I of the moving project was completed--5,800 volumes of the pre-1976 journals and indices/abstracts were moved to the basement. Phase II involving moving all the pre-1971 books is underway.
- o Since April 1986, on a twice-daily retrieval schedule, 347 volumes of journals were retrieved and reshelfed after use in the basement area. The requested journal titles were record. They will serve as a reference base for future planning to retain the most frequently requested journals on the main shelves for easy user access.
- o Last year, 555 books were checked out; 344 books from the Library and 211 from permanent loans in various laboratories.
- o Dial-in online access to the NIH Library's catalog has been in use.
- o The RICOH model FT 5070 copier has been well maintained in the Library. More than 250,000 copies were made on the machine this past year.

Animal Resources Section

The Animal Resources Section (ARS) is responsible for the supply of experimental laboratory animals supporting aging research at the GRC. These animals are supplied through inhouse production and via contracts.

Production and quality control programs are currently concerned with mice, rats, rabbits, dogs, monkeys, hamsters, and chickens. All animals are maintained under strictly controlled environmental conditions. In addition to the production and procurement of these animals, the majority are aged to the near limits of their life expectancy within the Center. Approximately 25,000 animals, supporting 50% of the research projects at the GRC, are issued and maintained by the Animal Resources Section.

Activities and Achievements

- o Maintained accreditation with the American Association for Accreditation of Laboratory Animal Care (AAALAC) for the ninth consecutive year.

- o Maintained institutional membership with the American Association of Laboratory Animal Science (AALAS), as well as with its local National Capital Area Branch (NCAB).
- o A total of 7,238 mice and rats, of varying ages, were issued from the aging colonies.
- o The Aging Wistar Rat Colony increased its issuance of animals by 17% over last year's total.
- o Over 100 hours were used to support 38 aseptic surgical procedures.
- o In addition to our stock animals, approximately 4,764 mice, 3,900 chicks, 3,244 rats, 178 rabbits, 21 Beagles, and 13 primates were received and housed by the ARS.
- o Animal technician training conducted at the GRC by the ARS supervisory staff resulted in national certification of one Laboratory Animal Technician and four Assistant Laboratory Animal Technicians.
- o To validate the housing and husbandry procedures of the Wistar Rat Colony, a two year experiment has been established to ascertain the minimum space requirements for rats.
- o The Aging Beagle Colony has doubled its size with the acquisition of 21 Beagles from the National Institute of Drug Abuse Addiction Research Center.
- o The ARS was able to supply approximately 200 aging rats to other institutions throughout the country for use in aging research efforts.

Instrument Design and Fabrication Section

This section provides technical support to GRC staff including the fabrication of mechanical assemblies; various building maintenance activities; and mechanical and electrical repairs to laboratory equipment.

Activities and Achievements

During the past year, along with numerous thirty minute to two hour repair or construction jobs, the section's technicians designed, fabricated, and installed equipment such as an MRI cradle for human limbs, rabbit cradles for spectroscopy and imaging, copper constant temperature chambers, and cell culture devices. Also, circuitry for MRI probes, electrophoresis trays for DNA studies, power injectors for micro-injections of aequorin into the heart muscle, a full size modular human maze, a beam-splitter, and worked on many other long-term projects.

ANNUAL REPORT OF THE LONGITUDINAL STUDIES BRANCH

NATIONAL INSTITUTE ON AGING

The Longitudinal Studies Branch (LSB), created in FY 1986, promotes and conducts multidisciplinary, longitudinal studies of physiological and behavioral changes with aging. It is responsible for the central administration and management of the Baltimore Longitudinal Study of Aging (BLSA), a longstanding research program of the Gerontology Research Center operated heretofore as one activity of another Laboratory. The LSB staff are responsible for recruitment and maintenance of the research participants in the BLSA, for entering, storing and retrieving BLSA data in computer based data banks, and for conducting research with the BLSA data and developing statistical methodologies appropriate to longitudinal studies. The BLSA is utilized by scientists in nine different sections of seven laboratories. To facilitate coordination of the diverse activities across the numerous organizations, the Chief, LSB also holds the title, Associate Scientific Director for the Baltimore Longitudinal Study of Aging, and in that capacity is assigned to the Office of the Scientific Director, NIA. The Associate Scientific Director, in concert with an internally comprised Steering Committee, is responsible for setting long term scientific goals for the BLSA as well as promoting and facilitating the use of the BLSA by scientists within and outside of the Gerontology Research Center.

The research objectives of the LSB relative to the BLSA are:

1. To perform studies of age-related changes in physiological and behavioral functions utilizing information collected on BLSA participants over the life of the Study, and employing whatever resources are appropriate to the subject matter;
2. To perform correlational and retrospective studies that relate BLSA data from various disciplines to one another and to various participant endpoints, e.g., disease, death, functional disabilities;
3. To develop and apply new statistical methodology and theory appropriate to longitudinal studies;
4. To promote and facilitate the use of the unique BLSA research resource by scientists both within the Gerontology Research Center and outside the Institute using either new information or existing data;
5. To develop long range scientific plans which will enhance the value of existing information and provide a scientifically sound basis for eliminating, adding or maintaining current test procedures; and
6. To provide a stimulating and challenging environment for the research training of scientists of any level whose educational needs can be met by the unique environment offered by a large scale multidisciplinary research endeavor.

The support of the six research objectives stated above requires a relatively complex administrative and management activity. The complexity alluded to results from the facts that: there are several hundred men and women scheduled for dozens of procedures on a recurring two year cycle of testing; there are dozens of investigators, some new and others more senior, whose activities are supported from time of research planning through data collection, storage, and utilization; and there is a very large data bank representing thousands of variables and spanning over a quarter century of data collection efforts.

The five administrative and management objectives for the LSB that support the six research objectives relative to the BLSA are:

1. To improve retention of current research participants in the BLSA through better feedback of information about themselves and the Study, better utilization of time and reduction of required paper work relative to forms and procedures, and improvements in the social and physical environment of the research setting;
2. To maintain the current number of under-75 male participants and to increase the number of female and over-75 male participants in the BLSA;
3. To improve the utilization of participant time in order to increase the opportunities for research as well as to increase participant satisfaction;
4. To improve the accuracy, accessibility and utilization of BLSA data stored in the computer-based data bank; and
5. To facilitate the use of the data from the BLSA by all investigators through consultation and assistance on statistical and computer methodology.

To accomplish its research mission, the LSB is organized into three functional units: Participant Scheduling and Testing, concerned with coordinating all and performing some of the testing during the two and one-half day visit of each participant; Data Management, concerned with entry, storage, and utilization of BLSA data and computer support of all research and administrative activities of the LSB; and, Statistical Sciences, concerned with the direction and conduct of data analyses, the development and application of statistical theory and methodology and consultation. Participant retention, recruitment and other related functions cross organizational lines and are coordinated through working groups and committees established by the Chief, LSB.

FY 1986 ANNUAL REPORT AND RESEARCH HIGHLIGHTS

The BLSA provides a dedicated and relatively well characterized group of subjects as a resource in support of a wide variety of scientific investigations in gerontology and other disciplines. The following paragraphs briefly describe the sample, the workload for the year, and a description of the research carried out, organized according to the research and administrative goals enumerated above. The research described refers only to a small part of the total output, the remainder of which is described in the reports of other laboratories.

The Study Group: BLSA participants are male and female volunteers recruited by other participants in the program. Recruits agree to return to GRC in Baltimore for 2½ days of testing every 2 years for an undetermined but hopefully long period of time. Our sample continues to be highly educated, mostly married, describing themselves as financially comfortable or better, and of the group who returned for the fifth visit, 90% rated their health as good or excellent on both first and fifth visits. Recent intake has focused on male and female volunteers 75 years of age and older.

Status: By August 6, 1986 a total of 1709 men and women (1262 men and 447 women) have participated in the testing program on one or more visits to the GRC for a total of 9934 visits since the inception of the program.

FY 1986 Workload: From October 1, 1985 to August 12, 1986, 14 women and 14 men were newly admitted to the program. Of the 447 women who have joined the BLSA since January 1978, 14 have died. Of the 1262 men who have joined the BLSA since the inception of the Study in 1958, 364 have died. The age and sex distribution of the active subjects is shown in Table 1. The distribution of original and repeat visits of females since 1978 is shown in Figure 1.

The total number of visits according to initial and repeat visit by calendar year is displayed in Figure 2. Although women were added to the Study in 1978, the total number of visits by men and women has remained fairly constant. The goal of having equal numbers of male and female participants is unattainable under present circumstances. In order to achieve the goal, a larger testing staff is necessary. There is no shortage of potential participants of either sex.

Table 1

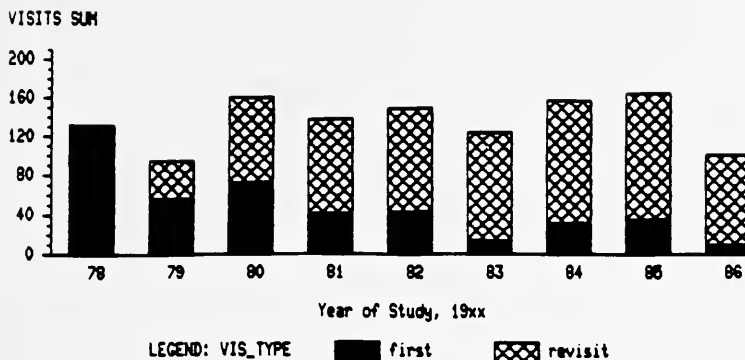
Distribution of Active BLSA Subjects by Age and Sex

6-Aug-86

Age Group		Males			Females		
at least	but under	#	% of sex	% of total	#	% of sex	% of total
	20	0	0.00	0.00	1	0.29	0.11
20	25	4	0.67	0.42	2	0.58	0.21
25	30	18	3.02	1.91	18	5.19	1.91
30	35	29	4.87	3.08	23	6.63	2.44
35	40	32	5.37	3.39	26	7.49	2.76
40	45	65	10.91	6.89	25	7.20	2.65
45	50	37	6.21	3.92	25	7.20	2.65
50	55	38	6.38	4.03	24	6.92	2.55
55	60	44	7.38	4.67	27	7.78	2.86
60	65	68	11.41	7.21	26	7.49	2.76
65	70	59	9.90	6.26	36	10.37	3.82
70	75	64	10.74	6.79	38	10.95	4.03
75	80	69	11.58	7.32	40	11.53	4.24
80	85	43	7.21	4.56	24	6.92	2.55
85	90	19	3.19	2.01	8	2.31	0.85
90	95	7	1.17	0.74	4	1.15	0.42
95		0	0.00	0.00	0	0.00	0.00
TOTAL		596	100.00	63.20	347	100.00	36.80

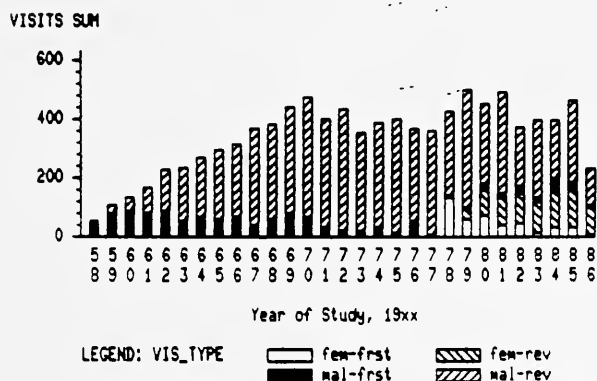
Female Participants

(FIGURE 1)



Participant Visits by Year

(FIGURE 2)



RESEARCH OBJECTIVE #1: To perform studies of age-related changes in physiological and behavioral functions utilizing information collected on BLSA participants over the life of the Study, and employing whatever resources are appropriate to the subject matter.

The research holdings of the BLSA include a number of data sets which have not been analyzed in sufficient detail to permit publication of basic descriptive findings or to allow for a scientifically sound basis for deciding to continue, modify, or discontinue data collection. To remedy this state of affairs, four data sets were selected from over a dozen identified that have substantial amounts of data available, that are labor intensive for testing staff and that have an uncertain status with respect to the question of need for further data. In order of the amount of analysis accomplished over the fiscal year from least to most, the four areas are pulmonary function, reaction time, hearing, and vision. In succeeding years, other areas will be substituted as analyses of these data are completed.

Pulmonary Function. Forced expiratory volume, vital capacity and maximum breathing rate have been measured on male and female participants almost since the inception of the BLSA. Analyses of cross-sectional data were first published in the 1960s by GRC staff and later as a result of a review of available data by investigators from The Johns Hopkins University School of Hygiene and Public Health. An investment in new equipment was made in FY 1985, and the GRC technician who collects the data received technical training in the same year. Yet, the relationship of current and planned data collection and analyses of current and previously collected data remained poorly defined at the beginning of the reporting period. To improve continuity between the collection and analysis of current and past data, an "investigatorship" and supporting technical group have been created using the talents of two nationally recognized authorities who are familiar with the data. As a result, a set of hypotheses now exists that guide the analysis of data; a plan of analysis is established which will make it possible to evaluate all of the accumulated and currently collected data using the same procedures; and procedures established that insure a high quality of control over the collection of data and their scoring and interpretation (initiated in August 1986). Retrospective analysis of existing data will be initiated in September 1986.

Reaction Time. Data on simple and two-choice reaction time have been collected since 1972. In one condition, BLSA participants press a hand held button as soon as possible whenever either a high or low frequency tone is presented. In contrast to this baseline condition, participants, in a choice reaction condition, press the button when the high frequency tone but not the low frequency one is presented. The comparisons of interest are the difference between the response times in the two conditions across age groups and in the age-related changes in reaction time on successive visits of the same participants. Analyses to date indicate that the age-related differences in response times obtained during first visits of participants increase with older age and that the absolute difference in reaction times between baseline and choice conditions does not vary across age.

These results, similar to other published data, are consistent with the hypothesis that the static, perceptual-motor part of the observed reaction times are primarily involved in the observed age differences in response speed, because the difference between the total response time for the choice and baseline conditions (the decision component) did not vary over age groups. There are sufficient data to permit the evaluation of four observations per participant for several hundred male participants. The results show clearly that age-related increases in reaction time occur in all age groups represented (20s through 80s). Somewhat puzzling is the finding that in several groups the final average reaction times of persons on their fourth visit was longer than that of the the next older cohort on their first. At present, a number of analyses are under way to see if the observed phenomenon is an artifact of procedural changes over the years. The results are of considerable interest to gerontologists because they represent the first substantial body of longitudinal data available to document age changes as opposed to age differences in reaction time.

Hearing. Serial observations of thresholds for continuous and pulsed tones have been obtained with a Bekesy Audiometer from several hundred male participants in the BLSA. The data consist of threshold intensities for each ear for each individual necessary for hearing 11 different frequencies ranging from 125 to 8000 Hz. First visit data from participants confirm previously reported cross-sectional results, demonstrating an increase in threshold with age that is greatest for high frequency tones. In the following account, data are described for 7 sub-samples of 10 males representing 7 age decades.

Each such hearing test may be represented satisfactorily by a non-linear relationship given by

$$Y = A + B \log x + C (\log x)^2$$

where Y represents the observed volume intensity in decibels for a given frequency X in hertz and log is the usual logarithm to the base e. The orderliness of the fitted data to the equation is striking. The equation also provides an excellent description of the reference data in the field.

An analysis of variance model is being developed to study the relative importance of the various types of possible variability arising in these data (e.g. left vs. right ear and condition of testing). Table 2 shows the results of an analysis of variance for a group of 10 eighty-year-old males having hearing tests taken at 80, 85 and 90 years of age.

The Table indicates large between-person variability as well as a large between-age variability indicating an important reduction in hearing perception as the 10 participants aged from age 80 to age 90. On the other hand, the variability between ears is negligible. This analysis allows us to investigate possible interactions between testing variables as well. Work is continuing on interpreting these findings.

TABLE 2

Within Group Analysis for Differences in Frequency, Age, and Ears
80 Yr. Old Males, Pulsating Tone

<u>Source of Variation</u>	<u>D.F.</u>	<u>Mean Square</u>	<u>F Test</u>
Overall Mean	1	1779132.38	--
Between Persons (Error)	9	6625.65	257.61**
Between Frequencies	10	15063.97	585.69**
Regression	2	73629.55	--
Error	8	422.58	--
Between Ages	2	8947.50	347.88**
Between Ears	1	0.88	<1.00
Frequency X Age	20	79.38	3.09*
Frequency X Ear	10	5.07	<1.00
Age X Ear	2	30.94	1.20
Person X Frequency	90	203.34	7.91**
Person X Age	18	563.53	21.91**
Person X Ear	9	10.85	<1.00
Higher-Order Interactive (Within-Person Error)	488	25.72	--

*P<0.001, **P<0.0001.

The model described above was used to compare initial values and those for 5 and 10 year follow-ups made on the same individual for right ear pulsed tone values. Representative results included a 37 db ($p < .001$) difference between initial thresholds for 400 hz between 20 and 80 year olds. The predicted 10 year change for 400 hz for 20 year olds was 13 db ($p < .001$) and 16 db for 80 year olds, respectively.

The results will be presented at the November 1986 meeting of the Gerontological Society of America.

Vision. Visual acuity with and without corrective lenses as assessed every two years for several hundred male and female volunteers in the Baltimore Longitudinal Study of Aging. A Titmus tester was used to assess Snellen acuities ranging from 20/15 to 20/200 (far) and 14/10.5 to 14/140 (near). Cross-sectional results for men and women were very similar to those previously reported. Ten-year longitudinal changes in acuities for 587 males representing age decades from the 20s to the 80s revealed significant declines in corrected as well as uncorrected acuity that was greatest in men initially in their 60s and 70s. The results were consistent with the hypothesis that less light reaches the retina of persons as they age. As expected, uncorrected near acuity declined precipitously between the 40s and 50s reflecting the age loss in accommodation. Within age groups, the declines in acuity were relatively greater for persons with better initial acuity. Cataracts and other optical pathologies contributed to but did not completely account for age-related changes in acuity. No significant cohort or time-of-measurement effects were observed over the 25 years during which acuities were measured. The results will be presented at the November 1986 meeting of the Gerontological Society of America, and a detailed report has been accepted for publication.

Parenthetically it should be noted that the analyses described above were accomplished by teams designated by the Chief, LSB. Each team consisted of the technician responsible for collecting the data, the Mathematical Statistician assigned to the Branch, a person from the Data Management Section, a GRC staff scientist if available, and one or more consultants engaged by the Branch to review the results of the analyses completed and to suggest other work necessary to complete an acceptable analysis of the data.

RESEARCH OBJECTIVE #2: To perform correlational and retrospective studies that relate BLSA data from various disciplines to one another and to various participant endpoints, e.g., diseases, death, functional disabilities.

Data from the BLSA is an example of prospective data involving multiple measurements taken at different times over the life of an individual with complications such as varying lengths of subject follow-up and irregular points of observation. The proportional hazards model as introduced by Cox and generalized by Kalbfleisch and Prentice is a stochastic model with wide-ranging and important implications for the analysis and interpretation of such data. This model has been successfully used to examine the problem of subject attrition in the BLSA. Factors have been identified which are associated with subjects dropping out of the BLSA. The initial model for this study of attrition has been extended to examine possible associations between the attrition of subjects recruited by other subjects in the Study and the attrition of each such subject recruiter in the Study. The proportional hazards model is also being used to examine the relationship between obesity and long-term mortality in the BLSA. The model is being developed so as to study such things as cigarette smoking as a confounding variable with body mass index (BMI) and the relationship of each to mortality, the possible influence of an individual's time of birth cohort on the model, and an examination of other related variables as well. After considering the aspects of the modeling just mentioned, one object of this analysis is to obtain relative risks and survival probabilities associated with different levels of the risk factors such as obesity and to examine how these relative risks change as an individual gets older. A manuscript entitled "A Longitudinal Examination of the Association Between Obesity and Mortality" was presented at the 1986 Annual Meetings of the American Statistical Association.

Efforts are also continuing in expanding the capabilities of the proportional hazards model to effectively use time-dependent covariates or risk factors, competing risks and multiple outcomes such as death due to different causes, and comprehensive and transparent graphic displays of results from the model.

RESEARCH OBJECTIVE #3: To develop and apply new statistical methodology and theory appropriate to longitudinal studies.

Research is being carried out involving simultaneous statistical inference or multiple comparisons. After estimates of desirable parameters or functions of parameters from specific models for data like those of the BLSA are obtained, it is often of interest to statistically test or compare differences among the different estimates. Decision theory along with Bayesian statistical theory is being used to develop innovative methods for performing multiple comparisons testing. Following an approach originally introduced by Duncan, our present work extends this early work to the solution of more complex simultaneous t testing, t interval and point estimation problems that arise in a wide variety of experimental situations. The Bayesian approach used, unlike traditional approaches, provides flexible (adaptive) a posteriori rules or procedures for relevant testing problems.

Decisions made about specific hypotheses can range from being highly conservative on the one hand to less conservative and highly powerful on the other, depending on certain statistics derivable from the data under consideration.

At present, a paper is being completed demonstrating how between-group and within-group comparisons can be made all at one time within a comprehensive Bayesian simultaneous testing plan. This work will enhance the ability to make comparisons between various groups of subjects observed during the course of a longitudinal study as well as comparisons in other data sets. In addition, computer software continues to be developed which will enhance the application of these methods.

Work in the area of the design of experiments is being carried out through the study of specific mathematical structure such as Latin squares, as well as higher dimensional structures which include cubes and hypercubes. Such structures allow experimenters to specify the randomization procedure necessary for the validity of statistical tests made in specific analyses of data. For example, in studies requiring repeated measures such as in longitudinal studies, Latin squares and frequency squares can be used to counterbalance order effects of such measurements. Research is being carried out in collaboration with G. L. Mullen of The Pennsylvania State University in which the VAX 11/780 of the Gerontology Research Center is used to study and classify various types of Latin and frequency squares needed in experimental designs. A paper presenting a comprehensive study of frequency squares has recently been published in Utilitas Mathematica (Vol. 29, 1986, pgs. 231-244) entitled "Some Results on Enumeration and Isotopic Classification of Frequency Squares" by L. J. Brant and G. L. Mullen. In addition, work is in progress on higher dimensional structures needed in the design of experiments with more than two control factors.

Other methodology is under consideration for application to longitudinal and cross-sectional data. These methods have been demonstrated with other researchers and scientists at the Gerontology Research Center and at the Center for Disease Control. A manuscript has been accepted for publication in Preventive Medicine which provides a method for analyzing a longitudinal disease control program which controls for the effect of staggered periods of observation for varying treatment groups. Other collaborative efforts have begun on longitudinal data from the BLSA dealing with tests of hearing perception and study attrition. Work continues on exploring the development of a model for classifying individuals into either a diseased or disease-free group based on dermatoglyphic characteristics obtained on each individual. In trying to develop some diagnostic index for a specific disease such as Alzheimer's disease, for example, based on dermatoglyphics, the first step undertaken has been to develop a classification method for differentiating individuals into the correct ethnic group based on dermatoglyphic characteristics. Using data from male subjects representing five different ethnic groups, several strategies for correctly classifying a given individual are being explored.

RESEARCH OBJECTIVE #4: To promote and facilitate the use of the unique BLSA research resource by scientists both within the Gerontology Research Center and outside the Institute using either new information or existing data.

During the reporting period several modifications and additions to existing protocols were made by GRC scientists who utilize the BLSA. In addition eight proposals for new research proposals were presented for consideration by the BLSA Steering Committee. Most involve collaborative efforts by GRC scientists and outside collaborators, although one was initiated collectively by LSB staff and members of the BLSA Steering Committee. Three of those which have been approved and/or implemented are described briefly below and others will be reported in the reports of other laboratories.

Autopsy Program. As a result of a collaborative arrangement with The Johns Hopkins University School of Medicine, we now offer BLSA participants the opportunity to have an autopsy performed following death. For participants within two hours driving time of The Johns Hopkins Hospital, Baltimore, the autopsy is performed at The Johns Hopkins Hospital. For those living farther away, the autopsy can be performed at a local facility using a protocol provided by the hospital. At present the autopsy consists of two parts: a brain autopsy developed by scientists working with the Alzheimer's Disease Research Center at The Johns Hopkins University School of Medicine, and a clinical autopsy to determine cause of death and the postmortem conditions of the major organ systems. At present GRC scientists in three laboratories are working to develop elaborations of one or both parts of the autopsy which will serve their research needs. As of August 18, 1986, two autopsies have been performed on deceased BLSA participants, 121 active participants have been presented with the concept during their current visit, and eight have made the arrangements to have an autopsy performed after their death, having taken the steps necessary to communicate their wishes to family who must legally authorize the autopsy and carry out related arrangements. It is expected that this program will open up a substantial array of research possibilities over future years.

Oral Physiology. The Clinical Director and scientific colleagues of the National Institute of Dental Research have initiated a reexamination of approximately 100 BLSA participants using a modification of a research protocol developed and used several years ago while the Clinical Director was a Staff Fellow at the GRC. This will provide longitudinal information on a variety of functions and structures of the oral cavity including salivary flow rate, oral motor function, taste thresholds and other sensory functions important to oral function. Since inception of the study in April 1986, eight BLSA participants have gone through the procedure.

Neurological Function. Staff neurologists at The Johns Hopkins University School of Medicine have outlined an elaborate range of research plans which will be phased into the study in a sequence of stages. The first part to be initiated consists of a neurological evaluation including mental status and gait that will result in

research quality diagnoses of disorders frequently related to aging. Subsequently it is planned to introduce a sophisticated assessment of gait in collaboration with GRC scientists and a study of the subtle distinctions between normal age-related changes in cognitive functioning and those associated with the earliest stages of dementia, again in collaboration with GRC scientists. As of August 18, 1986, 22 BLSA participants have undergone the clinical neurological evaluation.

Other projects that have been approved or which are awaiting outside funding for initiation include studies of osteoarthritis, effects of genetically determined capacity for acetylation of the liver on longevity and disease, prospective studies of the development of lenticular opacities, and validation of assessment of physical activity for studies of age differences in cardiovascular fitness and strength.

The above sample provides an impression of the range of activities that are proposed for use in the BLSA. All have or are planned to have a longitudinal component, a critical consideration in the decision of when to add a new procedure.

RESEARCH OBJECTIVE #5: To develop long range scientific plans which will enhance the value of existing information and provide a scientifically sound basis for eliminating, adding or maintaining current test procedures.

Functional Endpoints Of Old Age In Normal Aging. Mortality and morbidity are the traditional endpoints of prospective longitudinal studies such as the BLSA. While both endpoints are 'necessary' considerations in setting long term goals for the BLSA, neither are 'sufficient'. While definitively defined, death as an outcome has limited information to relate to the rich history accumulated over the typical period of study of BLSA participants. Likewise morbidity, the onset of disease, is limited inasmuch as the relationship between normal aging and disease itself is continuously undergoing change as a result of research such as the BLSA. Moreover, morbidity, as defined in terms of acute disease states, fails to take into account the array of chronic medical conditions which commonly accompany old age but which are not synonymous with it.

The BLSA provides an opportunity to refine measures of functional disabilities in several areas of everyday functioning which can in turn be related to the long history of information available on the participants. Such disabilities are sometimes the consequences of illnesses in old age and sometimes the precipitating factor in illness or the need for institutional care. Given the ability to define endpoints of functional disability, risk factor analysis and other statistical tools may be used to identify critical antecedents for such outcomes to the extent that they are measured in the BLSA.

Gender And Personality Differences In Aging. One of the potentially most useful conceptual tools for understanding normal aging is to compare patterns of aging in persons who vary in dimensions which themselves do not covary systematically with age. Examples include gender, socioeconomic status, formal years of education, and several dimensions of personality identified as being age-independent as a result of years of research at the Gerontology Research Center.

The availability of the classifying variables indicated above provides a basis for reviewing many of the findings from the BLSA which cut across disciplines. For example, age changes in osteoporosis, strength, metabolism, coping with challenges, and changes and losses in life are amenable to study. The differences in personality provide a basis for studying patterns of coping with disease states at different ages in both men and women and provide other ways of understanding age related changes in strength, mobility, time of onset of disease, etc. The operationalization of these ideas is a major priority for research during this year as well as the next.

Does The BLSA Have Indicators Of Successful Aging? Gerontological theory and speculation supported by observations of remarkable individual differences in the physiological and behavioral functioning among coevals by the calendar have resulted in the notion of successful aging to articulate differences between those who appear relatively robust and healthy in old age and those who seem relatively frail and sickly. The possible combinations of genetic, environmental and idiosyncratic factors that constitute the basis of successful aging are not understood. The concept has taken on such wide-spread interest among gerontologists that the theme of the November 1986 meeting of the Gerontological Society of America is called "Markers of Successful Aging."

The steps in giving operational definition to the concept of successful aging are to identify the characteristics of successful agers and then compare them to one or more comparison groups. This design differs from those in retrospective studies using risk factor analyses to help identify differences between a group of survivors and one or more comparison groups inasmuch as a working definition of the group of interest, successful agers in this case, is generated in advance. Within the BLSA several ways of identifying potential groups of successful agers are being considered. One that will receive initial attention is the comparison of participants who are known to be free of heart disease with those who are known to have occult heart disease and those who have clinically diagnosed heart disease. There are sufficient participants in similar age groups who can be compared on the array of information available. As a result, BLSA investigators can begin to explore the intriguing but as yet poorly defined questions about successful aging.

RESEARCH OBJECTIVE #6: To provide a stimulating and challenging environment for the research training of scientists of any level whose educational needs can be met by the unique environment offered by a large scale multidisciplinary research endeavor.

During the reporting period, two undergraduate mathematics students received research training and experience under the tutelage of the LSB Mathematical Statistician. Other scientists in a variety of laboratories use the BLSA resources, but their training is described elsewhere.

The LSB in conjunction with other laboratories is in a unique position to provide research training to physicians with interests in geriatrics whose training in this area has been largely clinical but who, because of their positions in academic medicine, need further research training. Examples of such physicians are the alumni of the Veterans Administration Geriatric Fellowship Program which provides two year post-residency clinical training. Over half of the physicians stay with the VA and teach in the VA affiliated medical schools. Advancement in their careers requires research activity for which they are often poorly equipped. Current experience makes it clear that the Baltimore Longitudinal Study of Aging provides an excellent source of training for such individuals.

The first priority of the LSB is to promote the use of the BLSA in research training conducted by other laboratories. The second priority is to promote training of statisticians. The third is to attract staff who would wish to be sponsored by the Chief, LSB.

ADMINISTRATIVE AND MANAGEMENT OBJECTIVE #1: To improve retention of current research participants in the BLSA through better feedback of information about themselves and the Study, better utilization of time, and reduction of required paper work relative to forms and procedures, and improvements in the social and physical environment of the research setting.

Several steps have been taken to improve retention of current participants through better feedback of information to them about themselves, particularly their health, and the results of the Study.

Information About Themselves. The average time elapsing from participant visit to the time the medical summary is sent to the participant or to the participant's physician has been cut from five months to less than four months. This is a marked improvement and results from more efficient administrative procedures and monitoring of goals set by the NIA Clinical Director prior to the reporting period. As a result of changes in the procedures for coding diagnoses adopted during the year, the figure will be improved further during the upcoming year. Medical problems of clinical significance continue to be communicated rapidly and effectively to participants and represent the largest basis for participant fan mail about the BLSA. The responsibility for communicating findings to the participant and the

participant's physician has been decentralized from the level of the Clinical Director to that of the senior physician who approves the letter prepared by the examining physician. As a result questions and requests for further information can be responded to much more rapidly.

Information About The Study. To improve feedback of information about and results of the Study, the participant newsletter now features a non-technical story about one of the major testing procedures experienced by the participants. The two latest issues included descriptions of the bone scanning study and the cardiovascular stress testing procedure. The newsletter also features a BLSA Director's report to the participants in which considerable information about the progress of the Study is presented. Much of the material developed for the newsletter is being incorporated into poster displays and video demonstrations of the procedures that participants can observe during their visits. Finally, the package of informed consent material has been edited and rewritten to improve the participant's understanding of the procedures and their scientific significance.

Copies of the recently published book, Normal Human Aging, were presented to all active participants. It is too technical for many readers. A contract has been let for development of a lay version of the book. It is expected that this will be ready for publication in the next fiscal year. In addition, a manuscript about findings from the Study was prepared for a major layman's scientific magazine. When published, the article will be an excellent lay summary of the major purposes and findings of the Study.

An effective way to provide information to the participants is through the program of shared lunch times between participants during their visits and 16 scientific and technical staff who take turns escorting participants to lunch. During a visit, a participant will meet between two and six staff depending on the duration of the visit and which staff are assigned for the day. The program is enjoyed by participants and staff alike.

Use Of Time. Inefficient use of time and heavy requirements for repetitious provision of information are frequently cited by participants as annoyances to them. The two are related. Two working groups have been established whose functions include identifying redundant information required of participants and the determination of information that can best be provided by selective updating of information previously provided by participants. The goal is to use available computer technology to provide testing staff and participants with preprinted information required for particular procedures which reduces the requirements for obtaining information unnecessarily in various testing procedures.

Environment. To improve the social and physical environment of the participants, staff have developed bulletin boards, created scrapbooks of participants and continue to be very attentive to participants' scheduling wishes, particularly with respect to groups that wish to make their visits at the same time. The arrangement for sharing lunch times with GRC scientific and technical staff has proven particularly

effective in making participants feel that they are "partners in research" in the BLSA. Finally, plans are in place to upgrade the hospital ward environment to motel standards as soon as resources are available.

ADMINISTRATIVE AND MANAGEMENT OBJECTIVE #2: To maintain the current number of under-75 male participants and to increase the number of female and over-75 male participants in the BLSA.

As indicated in the workload and sample size figures cited earlier, the BLSA has maintained a fairly stable testing schedule for the past few years. As testing slots open up, they have been used mostly for women. Our current goals are to recruit 4 new women a month and 2 new men. One of the main obstacles to increasing the number of women participants is the limitation in testing staff. We are currently surveying scientists to see what possibilities there are for staggering tests over 4 or 6 years rather than 2 and to try to increase the versatility of current testing staff so that more participants can be folded into the schedule.

Another concern is the characteristics of the new recruits with respect to the likelihood of frequency of return visits. To this end, research is being conducted on factors which are associated with dropping out of the Study.

In order to help minimize the attrition of Study participants, an investigation of factors related to Study attrition was initiated in June 1977. At that time, 1088 males had enrolled in the Study since its start in 1958. As of June 1977, 658 were currently active, 253 had dropped out of the Study and were still alive, and 177 were deceased. In the almost 10 years since that time, the Study population of males has increased by 174 (16%), the number of males dropping out and still alive increased by 49 (19%), and 187 (10.6%) more males have died. Many of the males who are listed as deceased dropped out of the Study before the date of their death. Also, during this time period, the BLSA was expanded to include 447 female participants. To date, 86 (19%) of these women have dropped out and 14 (4.1%) have died.

Work is in progress to do a longitudinal data analysis using the proportional hazards model to study the relationship between first visit characteristics and study attrition. Factors examined include health and financial status of participants, their age, place of residence, education, occupation, marital status, and method of recruitment into the BLSA. Also examined will be the status in the Study of recruiter and recruitees of participants, which is anticipated to be of importance in examining female participation in the Study since many of the female participants are either spouses or relatives of a male participant.

Based on preliminary analyses, factors believed to affect attrition in increasing order of importance for the males are age, education, distance from residence to GRC, self-health assessment and self-financial assessment. Attrition among the female participants is believed to be strongly affected by the status of associated male participants in the study. Thus associated male and female participants will make a joint decision to either remain or drop out of the Study

ADMINISTRATIVE AND MANAGEMENT OBJECTIVE #3: To improve the utilization of participant time in order to increase the opportunities for research as well as to increase participant satisfaction.

At present the participants are asked to spend two and one-half days on each visit. The number of testing hours currently assigned on each of the three days is 7, 8, and 3, respectively, on the first, second and third days. The 18 hours are unevenly divided among approximately 13 procedures.

To develop a baseline for improving use of participant time, the utilization of participant time was studied in the months of May, June and July of 1986. A total of 247 participants spent an aggregate of 1449 hours in BLSA procedures out of a total of 1731 available during the study period for an overall utilization rate of 85% of the total hours available. Further analysis indicated that the utilization of participant time varied considerably across the three days. On the first day, 100% of the seven scheduled hours were used. On the second day, 71% of the eight available hours were used. On the third day only about 11% of the participants stay and they are involved mostly in one procedure. Of the total three hours, only about 61% were used.

Two implications of this study are clear. Evening hours are available for further studies, and the entire half day is available for further testing for most persons. More tentatively, improved scheduling on the second day could open up as much as two and one-half hours on that day. These data are being used to determine ways in which more testing time could be created and that information communicated effectively to scientists who desire research time with BLSA participants. We also want to tell all participants in advance how long their stay will be.

ADMINISTRATIVE AND MANAGEMENT OBJECTIVE #4: To improve the accuracy, accessibility and utilization of BLSA data stored in the computer-based data bank.

Improvements in accuracy have centered around the issue of documentation. During the reporting period, the testing staff has developed documentation of the procedures they perform of sufficient quality so that they can be used by another technician to perform the same tests. They have also trained each other so that there is better staff backup during illness or vacation periods. The documentation contains instructions for coding of data into the computer.

A consultant who is expert in the areas of computer applications and data bases in medicine was engaged by the Branch to review all aspects of our computer operations. Among her 19 recommendations were several which concerned data quality control. Implementation of some of the recommendations in this area will require a high degree of cooperation between investigators from several laboratories, because the responsibility for accuracy of data entry ultimately devolves on the responsible investigator. However, several data entry programs have been devised to improve the accuracy and efficiency of keying in information.

The issue of documentation in computer programs has been addressed by developing and implementing for the first time documentation and programming standards. This is now of considerable importance because the Digital Equipment PDP 11/70 which is the repository for BLSA data contains several thousand routines for the manipulation of the data. The documentation and programming standards are particularly important to the more generally used of these routines.

Accessibility of data has received considerable attention although as indicated by our consultant, much more needs to be done.

A new menu structure has been implemented and installed which directs users to their desired applications more directly. Several administrative duties have been automated to improve their accuracy and to expedite their preparation, and a laser printer has been brought on-line which vastly improves the appearance of typed output. Utilities have been designed and added which standardize certain programming functions and provide feedback to the user. In the area of data quality, several new programs have been developed to look at the data base in different ways to ensure integrity. In all, several hundred new pieces of software have been developed. Many of these efforts have been translated into growth of the data base, which has expanded to about 852,000 records, or 7% larger than FY1985.

Accessibility to data also involves the Data General Eclipse system, which serves as a Remote Job Entry port to the large computer resource at NIH, Bethesda. It is maintained by LSB staff. The overall processing protocol for this machine had to be reworked due to a major change in DCRT billing procedures.

The LSB computer staff has also provided consultation on the NIH 370 computers and the GRC's VAX installation. We continue to provide support for the CDM clinical data base. Accessibility to medical records requires more compact storage and microfiche of the charts has proceeded at a very good rate.

Utilization of medical data will improve when the classification system of diagnoses is improved. To this end, the task of converting all 112,000 diagnoses on file from SNODO coding to ICD-9-CM began in August 1986 after LSB staff were trained in the use of ICD-9-CM. This will yield a more up-to-date reference which should be more useful to investigators. This task involves several stages. First, the SNODO will be reviewed for accuracy, then all SNODO codes will be researched to find its ICD-9-CM equivalent, which will then be input.

When the task is fully completed, these new codes will be retrofit into the master file in place of SN000 codes. In the interim, LSB staff have taken over the task of diagnoses encoding from the physicians, to ensure greater consistency in the final product.

ADMINISTRATIVE AND MANAGEMENT OBJECTIVE #5: To facilitate the use of the data from the BLSA by all investigators through consultation and assistance on statistical and computer methodology.

The statistical and computer staff of the LSB provide consultation and advice to the many laboratories that utilize BLSA data. The Branch statistician has provided an average of three consultations per week to investigators for a projected total of 150 for the reporting period. The three computer staff have provided an average of five consultations per week among them for a projected total of 250 per year. These activities are independent of the scientific activities in which they are active collaborators.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00015-28 LSB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Baltimore Longitudinal Study of Human Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory and institute affiliation)

J. L. Fozard

Chief

LSB, NIA

Other Investigators: See next page.

COOPERATING UNITS (if any)

LAB/BRANCH

Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

14.25

PROFESSIONAL

3.30

OTHER

10.95

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Baltimore Longitudinal Study of Human Aging (BLSA) serves as a resource for scientists working in the field of Gerontology. It provides a well-described group of men and women between 20 and 96 years of age for studies of the mechanisms of human aging. Projects in physiology, biochemistry, psychology, nutrition, pharmacology, endocrinology, and genetics, have been carried out or are in progress.

IRP-LSB-37

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00241-05 LSB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of Statistical Methodology for the Analysis of BLSA Data

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Larry J. Brant

Mathematical Statistician

CPB NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

0.7

OTHER:

0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The theoretical development of statistical methodology is progressing in the areas of epidemiological models, multiple comparisons, survival analysis, and the design of experiments, each of which is applicable to longitudinal studies. The research utilizes various regression methods for prospective studies, Bayesian theory in conjunction with decision theory, and numerical computing methods. The methodology created provides original contributions to experimental testing associated with longitudinal studies, the simultaneous comparison of specified effects (e.g. treatments against a control or placebo), epidemiological study of disease states, survival or failure analysis of longitudinal data and other longitudinal observations representing growth and other physical changes of humans and animals. Accomplishments in the creative use of Bayesian theory in the area of multiple comparisons will fill a void in the established statistical armamentarium.

ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

NATIONAL INSTITUTE ON AGING

I. SIGNIFICANT ADMINISTRATIVE EVENTS

The Laboratory of Behavioral Sciences (LBS) underwent major reorganization this year. Prior to this year, LBS included three sections: Psychophysiology, Learning and Problem Solving and Stress and Coping. Based on recommendations proposed by the Chief, LBS, the Learning and Problem Solving and the Stress and Coping Sections were transferred from LBS into a newly created Branch, The Laboratory of Personality and Cognition; and the Psychophysiology Section was disbanded and replaced by two sections: Behavioral Medicine and Behavioral Physiology. The primary reason for this reorganization was to establish LBS as a scientifically and conceptually coherent administrative unit in which the research programs derived from a consistent set of scientific principles.

One major step in this reorganization has not yet been completed. A chief of the Behavioral Medicine Section has not yet been selected. Three candidates have been interviewed within the past year, and other candidates are being considered. All of the candidates considered to date have been physicians trained in psychiatry. In each case, a major issue which has affected recruitment has been the problem of salary. Each of the candidates is actively engaged in clinical research, and each also is actively engaged in clinical practice. As is well known, physicians who are engaged in clinical practice often earn considerably more money than do physicians who are full-time researchers or teachers; and NIH salaries are not sufficient to match the income of practicing clinicians. Thus, while it is expected that a suitable candidate for the position of Chief of the Behavioral Medicine Section will be found within the next year, it is likely that financial constraints will limit the range of candidates.

II. SCIENTIFIC ACCOMPLISHMENTS

A. Behavioral Medicine Section

There are a four, active laboratories in this section, and each has a number of clinical studies going on.

1. The pulmonary program is studying the physiology of the chest wall muscles in various subject populations. One study is examining age differences among men and women, smokers and nonsmokers, and exercisers and nonexercisers during a standardized breathing task, 8 min of abdominal breathing. Abdominal breathing was chosen because of its clinical importance. Patients with obstructive lung disease often are trained to breathe abdominally; however, it is not clear what the cardiovascular and pulmonary demands of such performance are. Results to date indicate that abdominal breathing elicits cardiovascular and pulmonary responses similar to those elicited by an isometric and isotonic exercise challenge; that a significant number of people cannot maintain the task for the full 8 min interval; that smokers generally show poorer function than do nonsmokers; and that the cardiovascular effects are greatest in smokers who also are nonexercisers. A second study in the pulmonary program tested

professional opera singers using the same abdominal breathing task; this study has shown that professional singers, many of whom have been trained to breathe abdominally while singing, respond to the task like conditioned athletes; in contrast to the normal subjects they show very few cardiovascular or pulmonary effects in the task. Thus, these findings indicate that subjects can learn to perform abdominal breathing; however, one should consider abdominal breathing as an exercise skill which requires training, and which may be very difficult for patients with obstructive pulmonary disease to acquire.

2. The hypertension program is evaluating the clinical effectiveness of a Behavioral Stepped Care Program. One major study, which will be completed next year, is investigating the roles of self-monitoring of blood pressure, self-administered systolic blood pressure biofeedback and self-administered relaxation in the control of blood pressure. The study is controlled and includes three cohorts of patients: patients receiving only diuretic therapy; patients receiving beta-blocker therapy and patients receiving centrally or peripherally acting vasodilator therapy. Treated patients go through the Behavioral Stepped Care Program and are followed for at least one year after the completion of the program; control patients are referred to their regular physicians and are followed for comparable periods of time. The findings indicate that a significantly greater number of Stepped Care patients relative to control patients in the diuretic and beta-blocker groups, but not in the vasodilator group, can sustain major reductions in medication without significant increases in blood pressure. Thus, this study not only shows that the Behavioral Stepped Care Program is clinically effective, it also shows that the treatment is cost effective. A second, pilot study in this program is examining the application of the Behavioral Stepped Care Program in the treatment of isolated systolic hypertension. There are too few data to judge the effectiveness of the program; however, the pilot study will be completed within the next fiscal year, and if the results warrant it, a formal study will be implemented.

3. The outpatient, continence research program has been an outstanding success. Two studies published this year have shown: 1) Elderly patients with urinary stress incontinence, detrusor motor instability or urge incontinence can be trained--using bladder-sphincter biofeedback--to reduce the incidence of incontinent episodes by 82%, 85% and 94%, respectively. Furthermore, these patients learn rapidly, on average between 3 and 4, one hour training sessions; and they can learn and utilize these skills even in the face of antecedent strokes or concomitant diuretic therapy; 2) In the case of the stress incontinent patients, the bladder-sphincter biofeedback training increases the likelihood of successful learning significantly over education and training such as is done during training using Kegel exercises. On-going studies are finding that the techniques developed in LBS can be transferred to a clinical practice: 1) Collaborative research between LBS and the Beacham Ambulatory Geriatric Center of Francis Scott Key Medical Center is finding that a nurse/practitioner can administer the bladder-sphincter biofeedback program and/or other behavioral training procedures effectively and successfully; 2) In a program sponsored by the state of New Jersey, another nurse/practitioner who trained in LBS is successfully treating urinary incontinence in elderly persons using bladder-sphincter biofeedback; 3) A team of French geriatricians who visited LBS to learn our methods is now applying these techniques successfully to long-term care patients as well as outpatients in France, and has advised us that the French Government is considering a nation-wide effort to implement our treatments. There are other

on-going projects in this program which are noteworthy: 1) Many men become incontinent of urine following prostate surgery. These patients present with three distinct complaints, stress incontinence associated with specific behaviors, urge incontinence and continuous leakage (sometimes called total incontinence). Our studies indicate that these men can be trained to control their stress and urge incontinent episodes; however, continual leakage cannot be overcome; 2) There are very few systematic studies of toileting behavior. We are conducting two such studies. One is an assessment of the diurnal pattern of toileting behavior based on data derived from the BLSA participants during the period when they are at the GRC; and the second is a collaborative, questionnaire-based study of urinary habits of perimenopausal women which is part of a broader, epidemiological survey which was carried out in the greater Pittsburgh area; 3) The final project in this program is a study of behavioral treatment of urinary incontinence among elderly persons attending a hospital-based, day care center. A major finding from this project has been that incontinence is highly associated with mobility limitations; and the first study in this project showed that it is possible to increase walking behavior--especially walking to the toilet--among these clients.

4. The inpatient geriatric continence program is a major research effort co-sponsored by NIA and the Health Care Financing Administration (HCFA). The project is based at the Mason F. Lord (MFL) long-term care facility which is part of the Francis Scott Key Medical Center. The project includes a 15 bed research unit; however, the program is implemented throughout MFL. HCFA underwrites the incremental costs associated with nursing care on the research unit, and NIA underwrites the other costs associated with the program. Although this project has just begun--the first patients were admitted to the unit in December, 1985, preliminary findings suggest that many of the patients can and will respond to behavioral treatment programs. The data also indicate that an essential part of any program designed to increase continence among elderly, long-term care patients is staff management; specifically, practical programs must be devised which enable staff to better manage infirm, elderly persons. Our main focus in this program has been to train patients to increase the frequency of self-initiated toileting requests, and to train the staff to respond promptly to these requests as well as to establish regular toileting schedules for the patients. One major, incidental but noteworthy finding from this program has been the observation that families are reluctant to volunteer their elders for research, even when the research can benefit the participant: Among the 108 patients or families that we recruited, only 34% have agreed to participate. It would appear that an effort should be made to educate the public for the need for greater participation among the elderly in clinical studies. In addition to the continence project outlined above, this program has given rise to a number of corollary studies: 1) A survey carried out prior to the beginning of the project indicated that 82% of the patients in the nursing home were incontinent; that 75% of the incontinent patients were doubly incontinent; that 95% of the incontinent and 78% of the continent patients were mobility dependent, and 58% of the incontinent and 36% of the continent patients were cognitively impaired. It is especially noteworthy that 41% of the mobility impaired, incontinent patients are not cognitively impaired; 2) Another survey examined six different nursing tools that are used to assess behavioral problems among nursing home patients. This study revealed that the documentation of incontinence was very erratic; one tool, the Nurses Care Plan identified incontinence as a problem only 2.5% of the patients, whereas, the State Comprehensive Patient Appraisal, which is used to

establish the level of disability for Medicaid reimbursement purposes, identified incontinence in 94% of the patients; 3) Because mobility limitations underlie incontinence in so many patients, we have an enduring interest in optimizing mobility. One study, recently completed, has shown that many patients who use wheelchairs extensively can be reinforced to walk more often; that nurses aides and nursing staff can be trained to implement and manage this program; and that following such training, the patients will maintain increased ambulatory behaviors; 4) Finally, we also are looking at the effect of anti-psychotic medication on the behavior of nursing home patients. In one study, we have found a relatively high incidence of adverse behaviors such as noncompliance, aggression and diminished motor ability. We also have noted that treated patients sleep more than untreated patients; however, these same patients also have higher activity levels--including walking--when awake.

B. BEHAVIORAL PHYSIOLOGY SECTION

There are two major programs in this section.

1. The program on thermoregulation studies age changes in body temperature and age changes in the ability to respond to a cold challenge in the C57/Bl mouse. Previous research in this laboratory has shown that mice will habituate to cold challenges--biweekly exposure to 10°C cold for 3 hours; and that after three regularly scheduled exposures, these animals develop a stable response to the cold which reflects improved cold tolerance relative to the earlier exposures, but which does not improve further. A series of experiments carried out during the past year have shown: 1) If a 4th test is withheld, at the time of the 5th test, the animals show a dishabituation of cold tolerance such that performance on the 5th test is no better than on the first test; 2) Exposure to the test environment during the 4th test under conditions of room temperature does not prevent the dishabituation effect; 3) If 30 min of daily electrical stimulation of the brain in brain areas previously shown to maintain self-stimulation, are interpolated between the 3rd and 5th test, this will prevent the dishabituation effect; 4) 30 min, daily exposure to the experimental cages in which brain stimulation occurred will prevent the dishabituation effect. Future studies in this project will attempt to identify what skills are acquired in this situation, and how this learning fosters cold tolerance. Several projects are underway to identify the physiological mechanisms mediating age changes in body temperature and cold tolerance: one study is examining metabolic changes during cold exposure; a second study is exploring the role of interscapular, brown fat in thermoregulation; and a third study is using the technique of hypothalamic brain grafting to assess the role of central neural mechanisms in age changes in thermoregulation.

2. The programs in the nonhuman primate laboratory study the role of behavior in the regulation of cardiovascular function. Last year we reported that monkeys could learn to attenuate the tachycardia of exercise, and that trained animals showed evidence of more efficient cardiovascular and pulmonary performance during experiments in which they were slowing their hearts while exercising. Ongoing studies of the hemodynamic adjustments during exercise are providing additional evidence to support the notion of increased efficiency; not only is heart rate lower but cardiac output is greater and peripheral resistance is lower. Preliminary studies of central neural control mechanisms --"central command"--suggest that it may be possible to dissociate the exercise from other central neural control processes regulating heart rate. A second project in the nonhuman primate laboratory is examining diurnal

variations in hemodynamic functions. A previous report from this laboratory showed that there were distinct diurnal patterns in the integration of cardiovascular responses. Current research is extending these findings to other responses of the circulation. A major finding has been that there is a reliable diurnal pattern of change in total peripheral resistance. In each of three animals, each studied over three weeks, we have found a pattern of hemodynamic response throughout the night characterized by falls in heart rate, stroke volume, cardiac output and blood pressure. What is especially noteworthy about these findings is that while cardiac output and blood pressure fall, total peripheral resistance rises throughout the night and reaches its highest, sustained level from 1:00 AM until 7:00 AM. These findings take on particular significance in light of recent reports that people are most likely to experience catastrophic cardiovascular events such as myocardial infarction or sudden death at about 9:00 AM, shortly after awakening. Our data indicate that while cardiac preload is reduced throughout the night, cardiac afterload is greatly increased. If the pattern we observe in our animals also occurs in patients with heart disease, then it is possible that the sustained, elevated afterload which exists throughout the night may contribute to the risk of occurrence of a catastrophic cardiovascular event in the morning.

variations in hemodynamic functions. A previous report from this laboratory showed that there were distinct diurnal patterns in the integration of cardiovascular responses. Current research is extending these findings to other responses of the circulation. A major finding has been that there is a reliable diurnal pattern of change in total peripheral resistance. In each of three animals, each studied over three weeks, we have found a pattern of hemodynamic response throughout the night characterized by falls in heart rate, stroke volume, cardiac output and blood pressure. What is especially noteworthy about these findings is that while cardiac output and blood pressure fall, total peripheral resistance rises throughout the night and reaches its highest, sustained level from 1:00 AM until 7:00 AM. These findings take on particular significance in light of recent reports that people are most likely to experience catastrophic cardiovascular events such as myocardial infarction or sudden death at about 9:00 AM, shortly after awakening. Our data indicate that while cardiac preload is reduced throughout the night, cardiac afterload is greatly increased. If the pattern we observe in our animals also occurs in patients with heart disease, then it is possible that the sustained, elevated afterload which exists throughout the night may contribute to the risk of occurrence of a catastrophic cardiovascular event in the morning.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00063-19 LBS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Learned Modification of Visceral Function in Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

Mark I. Talan, M.D., Ph.D.

Visiting Scientist

LBS, GRC, NIA

COOPERATING UNITS (if any)

Laboratory of Cellular and Molecular Biology
University of California, San Diego Medical School

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Physiology

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS:

5.43

PROFESSIONAL:

1.83

OTHER:

3.60

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments we are studying the extent to which the cardiovascular system can be modified by instrumental conditioning. In other experiments we examine age-related changes in thermoregulation.

IRP-LBS-60

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00067-19 LBS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

Learned Modification of Visceral Function in Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.	Chief, LBS	LBS, GRC, NIA
Kathleen A. McCormick, Ph.D.	Research Nurse	LBS, GRC, NIA
Kathryn L. Burgio, Ph.D.	Staff Fellow	LBS, GRC, NIA
Michael S. Glasgow, Ph.D.	Research Physiologist	LBS, GRC, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center; CareFirst Medical Plan; New York Opera Company; Wolf Trap Farms; University of Pittsburgh School Of Medicine; BLSA.

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224.

TOTAL MAN-YEARS

7.38

PROFESSIONAL

3.08

OTHER

4.30

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is concerned with the application of behavioral methods and principles to clinical medicine. Subjects are patients selected from various medical clinics, or normal subjects who are studied to evaluate potential clinical methods. The main focus of this project is on clinical problems especially relevant to middle aged or elderly persons.

IRP-LBS-68

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00070-02 LBS

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders)

Behavioral Assessment and Treatment of Incontinence in Nursing Home Residents

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

Kathleen A. McCormick, Ph.D.

Research Nurse

LBS, GRC, NIA

Louis Burgio, Ph.D.

Psychologist

LBS, GRC, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center; Health Care Financing Administration;
Office of the Surgeon General of the United States.

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS

2.79

PROFESSIONAL

1.79

OTHER

1.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Incontinence is a major reason for institutionalizing elderly persons, and is widespread in nursing homes. This project is designed to evaluate behavioral intervention techniques for the treatment of these patients.

IRP-LBS-84

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00071-01 LBS

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isolated Systolic Hypertension

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

B. T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS:

.15

PROFESSIONAL:

.05

OTHER:

.10

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Isolated systolic hypertension is a common problem among elderly persons. This project is designed as a pilot study to estimate the clinical effectiveness of a behavioral stepped-care program to lower systolic pressure in these patients.

IRP-LBS-93

Annual Report of the Laboratory of Biological Chemistry
National Institute on Aging

The Laboratory of Biological Chemistry conducts basic research on the molecular basis of life processes. Studies are focused on the mechanisms of transport and metabolism, and the regulation of these systems by hormones, signal-transduction mechanisms, and pharmacological agents. Investigations describe how physiological control processes change with age and in age-associated disease, and determine the mechanism of the alterations.

The Laboratory of Biological Chemistry consists of two sections - the Regulatory Mechanisms Section, and the Membrane Biology Section.

The Regulatory Mechanisms Section investigates calcium and phosphate transport in relation to mineral homeostasis and age-associated osteopenia; and sodium, proton and other ion fluxes in relation to the control of intracellular and extracellular environments, acid-base balance and metabolism. Studies characterize the membrane and cellular transport systems and their control by hormones, pathophysiological effectors and pharmacological agents. Investigations describe how these regulatory systems are affected by age and by age-associated disease.

The Membrane Biology Section seeks to determine the chemical nature and sequence of intermediate reactions controlling the movement of cations through ionic channels and pumps. The behavior of these systems with respect to energy utilization and energy transduction, ion selectivity, gating mechanisms, and sensitivity to hormones and pharmacological agents are characterized. Studies concern how the affinity, capacity and selectivity of ion translocation mechanisms are affected by aging.

This report summarizes the following basic sciences projects:

1. The mechanism by which the action of parathyroid hormone (PTH) on Na^+ - Ca^{2+} exchange in renal cells is blunted in the aged rat. We previously reported that PTH modulated Ca^{2+} transport in the kidney by regulating $\text{Na}^+/\text{Ca}^{2+}$ exchange activity in the basolateral membrane (J. Biol. Chem. 259: 10827, 1984) and further, that the hormonal modulation was mediated by a cAMP mechanism and the PTH stimulations of Na^+ -dependent Ca^{2+} efflux and adenylate cyclase were markedly blunted in renal cortical cells from aged (24 month) rats compared to the transport in cells from 2, 6 and 12 month animals (J. Biol. Chem. 261: 5419, 1986). In contrast, forskolin-stimulated Na^+ -dependent Ca^{2+} efflux and adenylate cyclase were found not to change with senescence. These findings would be compatible with a mechanism of desensitization that occurred at the level of the receptor or hormone receptor coupling to adenylate cyclase.

The coupling of the PTH receptor to the catalytic unit of the adenylate cyclase complex is known to be mediated by two GTP-binding proteins, a stimulatory and a inhibitor protein, which react, respectively, with cholera toxin and pertussis toxin. We have used these probes to examine the activities of the GTP-binding proteins as a function of age. We have found that:

- (1) cholera toxin increased Na^+ -dependent Ca^{2+} efflux in cells from adult (6 month) rats, but not in cells from aged (24 month) animals;
- (2) pertussis toxin increased Na^+ -dependent Ca^{2+} efflux in cells from adult, but not aged, rats;
- (3) cholera toxin, pertussis toxin, PTH, GMP-PNP and NaF increased the intracellular cAMP content in cells from adult, but not aged, rats;
- (4) forskolin increased the cAMP content in cells from both ages;
- (5) the cholera toxin-mediated ADP-ribosylation of the 45 and 52 Kd polypeptide bands of the α subunit of the stimulatory GTP-binding protein was decreased 50% in the aged rat; and
- (6) the pertussis toxin-mediated ADP-ribosylation of the 41 Kd polypeptide band of the α subunit of the inhibitory GTP-binding protein was decreased 25% in the aged rat.

These findings suggest that the age-dependent blunting of the response of renal cells to PTH is due, at least in part, to decrements in the activities of the GTP-binding proteins of the adenylate cyclase complex.

2. Calcium absorption in isolated duodenal cells: the effects of age and 1,25-dihydroxycholecalciferol ($1,25\text{-(OH)}_2\text{D}_3$), the active hormonal form of vitamin D. Previous studies demonstrated an age-associated decline in calcium absorption in the intestine, a contributory factor to the negative calcium balance seen in the aged, and that $1,25\text{-(OH)}_2\text{D}_3$ functions as a major regulator of calcium absorption. We have initiated studies using isolated duodenal cells from the rat as a model to describe the biochemical basis of these phenomena.

We have found:

- (1) cellular uptakes (1 min) of Ca^{2+} were not different in rats 3, 6 and 12 months of age. At 24 month of age, however, Ca^{2+} uptake was significantly decreased, 3.24 ± 0.22 nmol/mg protein vs 4.70 ± 0.39 in cells from 6 month rats ($p < 0.01$);
- (2) the age-dependent decrement was specific for Ca^{2+} , no change was observed in the uptake of sugar;
- (3) the decreased Ca^{2+} uptake in senescent animals was not due to (a) a shift in the cell population from villus to crypt, (b) an altered cell volume, (c) an increase in rate of Ca^{2+} efflux, or (d) a change in the energy state of the cell, as indicated by cell ATP content;
- (4) kinetic analysis indicated that the decline in Ca^{2+} uptake in the aged was due to a decrease in the V_{max} of the system, the affinity for Ca^{2+} remained the same;

(5) the age-dependent decrease in cellular uptake was correlated with an age-dependent decrease in Ca^{2+} uptake by mucosal luminal (brush border) membrane vesicles;

(6) in vitro incubation of cells from 24 month old rats with $1,25-(\text{OH})_2\text{D}_3$ (10^{-13}M) increased Ca^{2+} uptake to the same level as found with cells from young adults, whereas in vitro incubation of the hormone with cells from 6 month rats did not affect Ca^{2+} uptake;

(7) in vivo administration of $1,25-(\text{OH})_2\text{D}_3$ to adult and aged rats increased cell Ca^{2+} uptake to the same level in both ages, and in vitro incubation of these cells with $1,25-(\text{OH})_2\text{D}_3$ did not enhance uptake further.

These findings demonstrate decreased Ca^{2+} uptake in duodenal cells from senescent rats and the correction of the age-related deficit with $1,25-(\text{OH})_2\text{D}_3$. The results are consistent with our observations, reported below, that renal mitochondria from aged rats have a decreased capacity to synthesize $1,25-(\text{OH})_2\text{D}_3$ and a lower serum level of the hormone.

Last year we reported an in vitro model system in which short-term (1 to 2 hr) incubation of $1,25-(\text{OH})_2\text{D}_3$ with isolated duodenal cells from vitamin D-deficient chicks increased cellular Ca^{2+} uptake by a protein synthesis-sensitive mechanism (J. Membrane Biol. 90:145, 1986). In continuing biochemical studies with this model, we found by Scatchard analysis that the nuclear receptor had a K_d of 0.6 nM and a capacity of 44 fmol/100 μg DNA. Sucrose density gradients indicated a single 3.5 S sedimentation coefficient for the chick intestinal receptor and DNA-cellulose chromatography of [^3H]- $1,25-(\text{OH})_2\text{D}_3$ binding complexes showed a major radioactive peak eluting at 0.28 M KCl in a linear salt gradient. The potency order for D_3 metabolites in inhibiting binding of [^3H]- $1,25-(\text{OH})_2\text{D}_3$ was $1,25-(\text{OH})_2\text{D}_3 > 1,24,25-(\text{OH})_3\text{D}_3 > 25-(\text{OH})\text{D}_3 > 1 \alpha (\text{OH})\text{D}_3 > 24,25-(\text{OH})_2\text{D}_3$.

3. Regulation of the synthesis of the Vitamin D hormone. A study of the effect of age on rat renal mitochondrial hydroxylation of $25-(\text{OH})\text{D}_3$, reported in part last year, was completed. In summary, we found a specific increase with age in 24-hydroxylase activity and a specific decrement with age in the basal activity of the 1-hydroxylase system. The latter finding correlates with the age-dependent declines in serum levels of the hormone and in intestinal calcium transport.

Studies were initiated on the biochemical mechanism for the regulation of Vitamin D hydroxylase activities using the isolated chick kidney cell as the experimental model (PNAS USA 72:3532, 1982). Preliminary findings indicated that cells from vitamin D replete birds had little or no 1-hydroxylase activity. Activity could be increased several-fold by incubating the cells with PTH. Cells from Vitamin D-deficient chicks had high 1-hydroxylase activity, which could be inhibited by prior incubation of the cells with $1,25-(\text{OH})_2\text{D}_3$.

4. Bone status in the aging rat. This year a new investigation was initiated in which we examined the biochemistry, mineral content and biomechanical properties of the femur of the aging rat. In males, the diaphyseal contents of calcium, phosphate and osteocalcin decreased significantly in the 24 month animal relative to the 6 and 12 month rat. Single photon absorptiometry at

femur midshaft revealed a small but statistically significant (-9%) decrease in bone density in the aged (24 month) compared to the mature adult (12 month) animal. Using the three point loading test, we found that the maximum breaking force required to fracture the femur at midshaft did not change with age. However, ultimate stress, a parameter which normalizes for differences in bone geometry, decreased 35% from the 12 month to the 24 month rat. This latter result could be explained by anthropometric data showing that cortical and medullary areas of the 24 month femur increased markedly (almost two-fold). Serum iPTH and osteocalcin levels almost doubled in the senescent rat. Serum calcium did not change with age, whereas serum phosphate decreased from the adult to the aged animal. These findings suggest that bone (femur) status is compromised in the aging male rat but that structural adaptations limit the impact of the decreased bone tissue integrity by maintaining the strength in intact femurs.

In females, diaphyseal calcium, phosphate and osteocalcin decreased with increasing age. Single photon absorptiometry did not reveal a significant change in bone density with age. However, total body calcium (determined by neutron activation), when normalized to body weight, fell with age. As with males, maximum breaking force was not altered in the aging female, but ultimate stress decreased 14% from 12 to 24 months. Other biomechanical parameters also declined in senescence, including yield and ultimate deformation, strain and modulus of elasticity. Anthropometry indicated an age-related increase in cortical area, but medullary area was unchanged.

5. Normal human bone cells in culture. We demonstrated that primary cultures of human bone cells could be established. Preliminary studies on the biochemistry and hormonal responses of the cells indicated their osteoblast-like character.

6. Patch-clamp studies in bone cells. A pioneering study was initiated to examine the ion channels responsible for the electro-conductive properties of osteoblast-like bone cells. Preliminary findings indicated that clonal cells from a rat osteosarcoma cell line (ROS 17/2.8) and cells from a primary culture of normal human bone possessed single channels which could contribute to Na^+ and K^+ permeabilities. A small channel, resembling the Ca^{2+} channel found in excitable tissues, was identified in ROS cells.

7. α_2 -Adrenergic hormones antagonized the response of renal cells to parathyroid hormone. A stable kidney cell line from the opossum (OK cells) was established in our laboratory. This cell line is unique because of its reported proximal tubule cell-like properties and possession of PTH receptors coupled to adenylate cyclase with high sensitivity. We used this cell system to confirm that PTH induced the accumulation of cAMP and inhibited Na^+ -dependent phosphate uptake. Then, we demonstrated that epinephrine, acting as an α_2 -adrenergic hormone, antagonized the responses of the cell to PTH.

The results (in the presence of propranolol) were:

	<u>cAMP formed</u> (pmol/dish)	<u>Phosphate uptake</u> (pmol/2min/mg prot)
Control	7.4 ± 0.5	1.57 ± 0.10
PTH	42.3 ± 2.4	1.18 ± 0.07
PTH + Epi	18.0 ± 1.9	1.26 ± 0.07
PTH + Epi + Yohimbine	36.5 ± 2.9	1.18 ± 0.07
PTH + Epi + Prazosin	20.0 ± 1.9	1.25 ± 0.8

We concluded: (1) The OK cell line had α_2 -adrenergic receptors; (2) α_2 -adrenergic agonists inhibited the cAMP and phosphate transport responses to PTH. Therefore, α_2 -adrenergic inputs may modulate phosphate transport in the kidney proximal tubule.

8. Effect of 1,25-(OH) $_2$ D $_3$ and age on tubular reabsorption of phosphate.

Serum levels of phosphate and calcium in vitamin D-deficient female rats were age-dependent: for phosphate, 2.64 mM and 0.92 mM, for 2-3 mo and 18 mo old, respectively; and, for calcium 1.24 mM and 2.42 mM, for the young and old, respectively. After the injection of 1,25-(OH) $_2$ D $_3$, serum phosphate concentration increased nearly 3-fold in the aged (low phosphate animals), but the concentration did not change in the young (high phosphate rats). Serum calcium levels increased in both age groups. The effect of vitamin D on maximum net tubular reabsorption of phosphate (max TR_{pi}/GFR) during acute phosphate infusion was also dependent on age (phosphate and/or calcium status). Vitamin D repletion increased max TR_{pi}/GFR in the older rat, whereas repletion had little or no effect on phosphate reabsorption in the young animal.

9. Thyroid hormone regulation of renal cell phosphate transport. In a study of the mechanism by which thyroid hormone regulated phosphate reabsorption in the kidney, it was found that triiodothyronine and L-thyroxine stimulated the Na⁺-dependent phosphate uptake system in primary cultured chick renal cells. Na⁺-independent phosphate uptake and Na⁺-dependent uptakes of α -methylglucoside and L-proline were unaffected. The increase in Na⁺-dependent phosphate uptake was concentration-dependent, exhibited an induction period, and was blocked by inhibitors of RNA and protein synthesis. The stimulation of phosphate uptake by triiodothyronine was due to an increased V_{max} rather than an altered affinity for phosphate. These findings demonstrated that thyroid hormone acted on renal cells to modulate phosphate transport and suggested that the renal cell system might serve as a model to examine the mechanism by which thyroid hormone controls gene expression and regulates plasma membrane transport function.

10. Parathyroid hormone (PTH) regulation of cytosolic Ca²⁺ in proximal tubules.

PTH caused a rapid, transient rise in cytosolic Ca²⁺ (determined by Quin-2 fluorescence) in rat proximal tubules, followed by a fall to a lower, sustained level. Both norepinephrine and angiotensin II caused somewhat faster and larger changes. Prior treatment with either agonist prevented any effect of PTH, while pretreatment with PTH followed by norepinephrine or angiotensin II diminished, but did not block, the effect of the latter agonists. The full response to PTH required the presence of extracellular calcium. Tubules pre-labeled with [³H]inositol and exposed to norepinephrine and PTH increased their levels of IP₁, IP₂, and IP₃ with generally comparable concentrations of hormones that produced changes in cytosolic Ca²⁺. Forskolin and dibutyryl cAMP failed to

elicit changes in cytosolic Ca^{2+} . These data indicated that PTH increased cytosolic Ca^{2+} by a cAMP-independent mechanism, one that appeared to involve phospholipase-C stimulated hydrolysis of polyphosphoinositides.

11. Regulation of protein kinase C. The effects of norepinephrine and phorbol esters on membrane-associated protein kinase C in proximal tubules and cardiac myocytes were studied. Phorbol myristate acetate (PMA) increased membrane-associated protein kinase C to 50-60% of total activity in both systems, while α_1 -adrenergic agonists produced somewhat smaller translocation. Both PMA and α_1 agonist stimulation were potentiated in myocytes by agents (KCl, ionomycin) that elevated intracellular Ca^{2+} , while removal of extracellular Ca^{2+} blunted the response in both myocytes and tubules. Effects of mitogens and PMA on protein kinase C were assessed in lymphocytes from young and old mice. While PMA-induced translocation was similar in splenic G_0 T-lymphocytes from young and old mice, concanavalin-A induced translocation was diminished approximately 50% in 24 mo mice compared to 6 mo animals.

12. Na^+ - H^+ exchange activity decreased in the senescent rat.

Amiloride-sensitive Na^+ - H^+ exchange activity in brush border membrane vesicles isolated from male rat proximal tubules was decreased in the senescent rat (24 month) compared to the young adult (6 month). There was no significant loss in Na^+ - H^+ exchange activity in the kidneys of animals between 6 and 18 months of age. Amiloride-insensitive Na^+ uptake and the rate of pH gradient dissipation were not altered by age. Sodium-dependent phosphate transport decreased progressively during the aging continuum. Sodium-dependent glucose transport was not significantly altered by age. Thus, in aging changes in renal plasma membrane transport functions followed distinct patterns. The decrease in Na^+ - H^+ exchange activity during aging contrasted with the increase in exchange activity reported previously in acute ablation models of chronic renal failure.

13. Mechanism of the renal response to an acid load in aging. Because in the kidney the Na^+ - H^+ exchanger has a critical role in the regulation of intracellular pH, the transepithelial transport of Na^+ and HCO_3^- , the acidification of the urine, and the urinary excretion of titratable acids and NH_4^+ , we examined the renal response to an acid load ($0.25 \text{ g NH}_4\text{Cl} \cdot \text{kg body wt}^{-1}$ as a 10% solution twice a day) in both young and old rats. (All rats had plasma creatinine values of $< 2 \text{ mg\%}$; senescent rats with higher plasma creatinine levels did not survive the acid loading.)

We have found:

- (1) after the acid load, blood pH was lower in the 24 month rat;
- (2) phosphate excretion was greater in the 24 month rat compared to the 6 month animal and increased in both after the acid load;
- (3) in non-acidotic rats, brush border membrane vesicle Na^+ -dependent phosphate uptake was lower in 24 month than in 6 month animals despite a decreased plasma phosphate and the acid load decreased phosphate uptake in both ages;

(4) amiloride-sensitive Na^+ uptake (Na^+ - H^+ exchange) in brush border membrane vesicles increased in response to the acid load in both age groups;

(5) although plasma calcium was the same in both age groups, calcium excretion was greater in the 24 month rat and increased after an acid load in both 6 and 24 month rats;

(6) NH_4 excretion increased more after an acid load in 6 month than in 24 month rats; and

(7) titratable acid excretion increased to equivalent amounts in both 6 and 24 month rats after the acid load but the 24 month rats excreted more under control conditions.

These findings demonstrate that the senescent rat excreted less NH_4 relative to titratable acids, as was found previously in the aged man. Therefore, the senescent rat might provide a good model for further studies on the mechanism of the renal response to an acid load during aging.

14. Thyroid hormone regulation of Na^+ - H^+ exchange activity. Last year, we reported that Na^+ - H^+ exchange activity in renal proximal tubule brush border membrane vesicles was increased in the hyperthyroid rat and decreased in the hypothyroid rat, relative to the euthyroid animal. The kinetic mechanism for increased exchange activity was also investigated. We concluded that the carrier density in the membrane or the velocity of the rate limiting step was regulated by thyroid hormone. We sought to distinguish between exchanger density in the membrane and a change in the rate limiting step by studying the effect of thyroid hormones on the transient kinetics of the exchange. Using low temperature (0°C) to resolve the initial time course of Na^+ uptake, we observed the presence of an early burst phase that was representative of the first turnover of the system and was proportional to the exchanger site density. A model for Na^+ transport via the exchanger was developed that included relatively slow reaction rates before and after Na^+ translocation. The slowest step followed Na^+ translocation. When we compared the Na^+ transient kinetics in membranes isolated from hyperthyroid and euthyroid rats, the data were best fitted by a model that showed a change in rate of the rate limiting step and not a change in the site density of the exchanger.

15. Biochemical characterization of the Na^+ - H^+ exchange carrier. Studies were initiated to identify the Na^+ - H^+ exchange carrier using an approach to selectively label the protein with an irreversible amino acid specific reagent. The carboxylate reactive reagent $\text{N,N}'$ -dicyclohexylcarbodiimide (DCCD) was tested. Preincubation of membrane vesicles with DCCD resulted in a 90% inhibition of Na^+ uptake and a corresponding decrease in the rate of pH gradient dissipation. The inhibition was blocked by Na^+ , Li^+ and amiloride. Exogenous nucleophiles reduced the inhibition. The rate of inactivation of the exchanger by DCCD followed a pseudo-first order reaction. We conclude that a single carboxylate selectively accessible to DCCD, or an amino acid which was cross-linked to the carboxylate by DCCD, was required for Na^+ - H^+ exchange activity.

16. Pharmacological studies of the calcium-activated potassium channel in cultured medullary thick ascending limb cells. Ca^{++} -activated K^+ channels with single channel conductances of $127 \pm \text{pS}$ were identified in the apical cell membrane of clone A₃ of cultured medullary thick ascending limb (mtal) cells. The channels were activated both by increasing Ca^{++} concentrations in the intracellular solution or by depolarizing the intracellular face. To determine the properties of these channels the influence of specific blocking agents on channel kinetics was determined. Both Ba^{++} and the scorpion toxin, charybdo-toxin (CTX), were slow blockers of the channels. $0.1 \mu\text{M}$ Ba^{++} applied to the intracellular face caused a 50% reduction in fractional open time (f_v). Ba^{++} block was both concentration and voltage dependent. Concentrations of CTX as low as 2 nM in the extracellular solution caused a significant reduction in f_v . Tetraethylammonium (TEA) and quinine were fast blockers of Ca^{++} -activated K^+ channels in mtal cells. Micromolar amounts of quinine applied to the intracellular face caused the channels to flicker rapidly between open and blocked states. Thus, these four blockers of Ca^{++} -activated K^+ channels in cultured mtal cells had distinctive blocking characteristics which might be used to identify these channels.

17. Calcium release channels in sarcoplasmic reticulum. Studies of Ca^{2+} -selective channels in skeletal muscle sarcoplasmic reticulum utilizing the patch-clamp technique demonstrated that the kinetic constants controlling the opening and closing of the channel were voltage-dependent. The steepness of the voltage dependence raised the possibility that transient membrane depolarization might play a role in Ca^{2+} release leading to tension development in muscle.

18. Transient kinetics of calcium translocation in the cardiac sarcolemma. Transient-state mixing experiments measuring Ca^{2+} translocation in cardiac sarcolemmal vesicles led to the demonstration of parallel components of Ca^{2+} flux corresponding to the activity of the Na^+ - Ca^{2+} exchanger operating in an uncoupled mode and of a Ca^{2+} channel that inactivated with time. The latter pathway might contribute to charge movement associated with the cardiac action potential.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00051-06 LBC
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Phosphate and Calcium Homeostasis: Pathophysiology of Osteopenia in Aging		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Bertram Sacktor Chief, Laboratory of Biological Chemistry LBC GRC NIA C. Tony Liang Research Chemist LBC GRC NIA Bernard A. Bulos Research Chemist LBC GRC NIA Linda Cheng Research Chemist LBC GRC NIA Gary Kiebzak Senior Staff Fellow LBC GRC NIA Sandra Guggino Senior Staff Fellow LBC GRC NIA Hiroyuki Hanai Visiting Fellow (EOD 9/01/84) LBC GRC NIA Shoshi Takamoto Visiting Fellow (EOD 4/04/85) LBC GRC NIA Isaac Meller Visiting Associate (EOD 7/11/86) LBC GRC NIA		
COOPERATING UNITS (if any) E. Kraus Renal Division, Department of Medicine JHU M. Levine Endocrine Division, Department of Medicine JHU V. Riley Department of Orthopedic Surgery, JHU, Baltimore MD cont'd		
LAB/BRANCH Gerontology Research Center, Laboratory of Biological Chemistry		
SECTION Regulatory Mechanisms Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, MD 21224		
TOTAL MAN-YEARS: 10.3	PROFESSIONAL: 7.3	OTHER: 3.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>This report describes studies on calcium and phosphate metabolism relevant to mineral homeostasis in aging and age-associated osteopenia. The findings summarize investigations on:</p> <ol style="list-style-type: none"> 1. The mechanism by which the action of parathyroid hormone (PTH) on Na^+-Ca^{2+} exchange in renal cells is blunted in the aged rat. 2. Calcium absorption in isolated duodenal cells: the effects of age and 1,25-dihydroxycholecalciferol ($1,25\text{-(OH)}_2\text{D}_3$), the active hormonal form of vitamin D. 3. Regulation of the synthesis of the Vitamin D hormone. 4. Bone status in the aging rat. 5. Normal human bone cells in culture. 6. Patch-clamp studies in bone cells. 7. α_2-Adrenergic hormones antagonized the response of renal cells to parathyroid hormone. 8. Effect of $1,25\text{-(OH)}_2\text{D}_3$ and age on tubular reabsorption of phosphate. 9. Thyroid hormone regulation of renal cell phosphate transport. 		

IRP-LBC-104

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00052-06 LBC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pathophysiological and Hormonal Regulation of Membrane Transport Systems

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bertram Sacktor	Chief, Laboratory of Biological Chemistry	LBC GRC NIA
C. Filburn	Research Chemist	LBC GRC NIA
J. Kinsella	Research Physiologist	LBC GRC NIA
S. Guggino	Senior Staff Fellow	LBC GRC NIA
R. Prasad	Visiting Fellow	LBC GRC NIA

COOPERATING UNITS (if any)

T. Kaku	Visiting Fellow	LCS GRC NIA
J. Proust	Visiting Associate	LCP GRC NIA
A. Nordin	Research Immunologist	LCP GRC NIA

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Regulatory Mechanisms Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

6.5

PROFESSIONAL:

4.0

OTHER:

2.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

This report describes studies on sodium, proton, potassium, calcium, and other ion fluxes in relation to the control of intracellular and extracellular environments, acid-base balance and metabolism; their control by hormones, pathophysiological effectors and pharmacological agents; and how these regulatory systems are affected by age and by age-associated disease. The findings summarize investigations on:

1. $\text{Na}^+\text{-H}^+$ exchange activity decreased in the senescent rat.
2. Mechanism of the renal response to an acid load in aging.
3. Thyroid hormone regulation of $\text{Na}^+\text{-H}^+$ exchange activity.
4. Biochemical characterization of the $\text{Na}^+\text{-H}^+$ exchange carrier.
5. Parathyroid hormone (PTH) regulation of cytosolic Ca^{2+} in proximal tubules.
6. Regulation of protein kinase C.
7. Pharmacological studies of the calcium-activated potassium channel in cultured medullary thick ascending limb cells.

IRP-LBC-112

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00048-12 LBC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Ion Transport Mechanisms and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Jeffrey P. Froehlich Medical Officer, Chief, Membrane Biol Sec

LBC GRC NIA

Other:

Phillip F. Heller

Chemist

LBC GRC NIA

Kinya Otsu

Visiting Fellow (EOD 12/1/84)

LBC GRC NIA

Sandra Guggino

Senior Staff Fellow

LBC GRC NIA

Bertram Sacktor

Chief, Laboratory of Biological Chemistry

LBC GRC NIA

James Kinsella

Research Physiologist

LBC GRC NIA

cont'd

COOPERATING UNITS (if any)

Laboratory of Neurosciences, NIA, NIH, Bethesda, MD.

Laboratory of Neurochemistry, NINCDS, NIH, Bethesda, MD.

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Membrane Biology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

4.3

PROFESSIONAL:

3.6

OTHER:

0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project focuses on the active and passive transport mechanisms involved in the formation and dissipation of ion gradients across cellular membranes. Patch-clamp studies on the Ca^{2+} -selective channel in skeletal muscle sarcoplasmic reticulum have demonstrated that the mean channel open time and bursting frequency are voltage-dependent. The inverse relationship between these parameters is compatible with a linear 3 state model for activation in which the channel may enter a second closed (inactivated) state or return to the original resting state upon leaving the open state. A positive correlation has been found between the disappearance of oxalate-facilitated Ca^{2+} loading and a 95 kilodalton protein in SR vesicles washed in hypotonic K^+ -free medium. Sodium ion-independent Ca^{2+} accumulation by cardiac sarcolemmal vesicles has been resolved into two distinct components: (1) carrier-mediated Ca^{2+} uptake by the Na^+ - Ca^{2+} exchanger operating in an uncoupled mode, and (2) channel-mediated Ca^{2+} translocation by a time-dependent Ca^{2+} channel. The latter pathway may contribute to the transient inward current of the cardiac action potential. Transient state measurements of Na^+ uptake by the Na^+ - H^+ exchanger in kidney brush border vesicles have uncovered new evidence for the participation of multiple Na^+ binding sites in the initial transport cycle and have allowed estimation of the carrier site density. Differences in the kinetic behavior between the first and subsequent turnovers of the Na^+ - H^+ exchanger support the existence of a unique pathway in the transport mechanism. Quenched-flow experiments with the CaATPase from skeletal SR have demonstrated complex effects of Iris and K^+ ions on the enzymatic partial reactions possibly reflecting changes in the extent of subunit association.

TRP-LBC-118

ANNUAL REPORT OF THE LABORATORY OF CARDIOVASCULAR SCIENCE
NATIONAL INSTITUTE ON AGING

The overall goals of the Laboratory of Cardiovascular Science are (1) to identify age-related changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to study myocardial structure and function, and response to pharmacological therapeutics in mechanical overload, altered thyroid state, and physical conditioning models, and to determine how age interacts with these altered cardiac states to determine the level of myocardial function; and (3) to study basic mechanisms in excitation-contraction coupling and of energy-yielding oxidative pathways in cardiac muscle. In meeting these objectives, studies are performed in human volunteers, intact animals, isolated heart and vascular tissues, isolated cardiac cells, and subcellular organelles.

Cardiac Function Section

Research of this Section is in both human and animal models and in tissues and cells from animal models. Our studies in man utilize state of the art technology to study the impact of age on cardiovascular function at rest and during exercise stress, when adrenergic modulation of the circulatory system is maximum. Subjects for this research are drawn from participants in the Baltimore Longitudinal Study of Aging (BLSA). Our purpose is not only to describe age-related changes per se but to determine mechanisms that underlie these changes. To meet this purpose, pharmacologic perturbations are employed in these studies, particularly those that pertain to the cardiovascular autonomic modulation. In animal models (rat and beagle dog), a more specific mechanistic approach is taken to investigate the direct effects of aging, cardiovascular overload state, physical conditioning, and pharmacologic perturbations on myocardial and vascular tissues. In addition, mechanisms of excitation-contraction coupling are explored in these isolated tissues. More specific yet are our studies on single cardiac myocytes, particularly those that deal with the regulation of cytosolic Ca^{2+} , and Ca^{2+} -induced Ca^{2+} release as a mechanism to couple excitation-contraction, and as manifest in spontaneous diastolic Ca^{2+} oscillations, as a potent modulator of both systolic and diastolic function, particularly in disease states when control of cell Ca^{2+} regulation may be deficient. Finally, studies in cardiac subcellular organelles, e.g. myofibrils, sarcoplasmic reticulum, probe the effects of aging, chronic physical conditioning, and cardiac overload states. This approach, in some instances, results in unique "vertical data" from man to organelle, e.g. those studies of autonomic modulation of cardiac function and its modification due to aging.

Energy Metabolism and Bioenergetics Section

The objective of this Section is to identify and characterize mechanisms whereby oxidative metabolism is enhanced in response to the energy-demands created by the increased performance of work; further, it is our endeavor to describe derangements in these control mechanisms which may occur during aging. Many of our studies involve cardiac muscle preparations, and the energy-demands reflect mainly those of contraction. In this case, the Ca^{2+} ion which forms the link between excitation and contraction also activates mitochondrial substrate oxida-

tion and therefore energy-provision, a relationship which we have recognized in the phrase "excitation-contraction-metabolism coupling." Studies are carried out at the level of isolated cardiac myocytes, isolated mitochondria and purified enzymes. As many of the animal-model studies of the Cardiac Function Section are concerned with the role of Ca^{2+} ions in stimulating contraction, our work is complementary, and there is scope for the closest interaction between the Sections. Other experimental paradigms being pursued in this Section include the stimulation by Ca^{2+} -mobilizing hormones of the energy-requiring gluconeogenic pathway in hepatocytes, and the role of Ca^{2+} ions in activating the synthesis of the neurotransmitter acetylcholine, as well as in the mediation of its release. The latter studies are carried out with preparations of presynaptic vesicles and are currently the focus of the aging studies of the Section.

During FY 1986, our studies have continued to range in scope from man to mechanistic studies of myocardial contraction and cell energetics.

Studies in Man

Exercise-induced Arrhythmias in Diuretic-Treated Subjects with Hypertension

Major controversy has recently arisen regarding a possible exacerbation of sudden cardiac death in hypertensive individuals treated with diuretics. To investigate a possible etiologic mechanism for such an outcome, we compared the prevalence and complexity of exercise-induced arrhythmias in BLSA subjects on chronic diuretic monotherapy for untreated hypertension with that in normotensive control group. Although the prevalence of exercise induced arrhythmias was higher in the diuretic treated group (D) than in controls (C) 57% versus 38%, $p < .05$, this difference was due entirely to the higher prevalence of simple ventricular ectopic beats (VEB) 44% versus 26%, $p < .05$. No difference between the groups was found in the prevalence of frequent or complex ectopic beats. Furthermore, within the D group, no difference in the occurrence of ectopic beats was found between men and women, those with resting ECG abnormalities and those without or between those with serum $\text{K} < 3.7$ versus those with higher serum K .

Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm. To assess the ability of maintenance digoxin therapy to improve exercise tolerance in patients with stable CHF, systolic dysfunction and sinus rhythm, we performed maximal treadmill exercise tests in 12 such individuals while monitoring respiratory gas exchange. No difference in exercise duration, maximal oxygen consumption ($\text{VO}_{2\text{max}}$), maximal heart rate, or ventilation was found after 4 weeks of digoxin versus 4 weeks of placebo in a randomized crossover study. During maximal upright bicycle exercise, however, digoxin increased ejection fraction from .26 to .31 despite identical exercise tolerance.

Our group has initiated the development of a questionnaire in conjunction with experts in cardiology at different universities to sample representative groups

of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. Among 2704 questionnaire respondents, diuretics alone were considered the best initial therapy for CHF in 50%, digitalis alone by 8% and the combination in 33%. Two thirds of the sample felt that digitalis improved exercise tolerance. Thus, despite growing evidence that digitalis glycosides can be successfully withdrawn from patients with chronic stable CHF, there is widespread belief that these drugs are effective in most CHF patients.

Complication of Maximal Treadmill Exercise in Apparently Normal Subjects

We have assessed the prevalence of exercise-induced ventricular tachycardia, exercise-induced supraventricular tachycardia and post-exercise hypotension in BLSA volunteers without clinical evidence of heart disease.

Out of 925 subjects undergoing maximal treadmill exercise between September, 1977 and December 1983, 10 subjects (1.2%) developed nonsustained ventricular tachycardia (VT) during or after exercise. Episodes varied in length from 3 to 6 beats and were near associated with symptoms. The prevalence of VT was 3.8% in subjects aged 65 and older. Over a follow-up period averaging 2.0 years, no subject with exercise-induced VT developed syncope, pre-syncope, angina, myocardial infarction or sudden death.

Exercise-induced supraventricular tachycardia (SVT) occurred in 50 subjects (5.3%). All episodes were paroxysmal atrial tachycardia; heart rate varied from 120 to 250 bpm ($\bar{x} = 175 \pm 40$). Of the 70 episodes of SVT, only 12 were ≥ 10 beats in length; 4 of these were associated with symptoms. The prevalence of SVT was 12.7% in the 245 subjects ≥ 65 years old but only 2.7% in those < 65 years. An ischemic ST segment response to exercise occurred in 14% of subjects.

Hypotension following treadmill exercise, defined by a fall in systolic blood pressure (SBP) at least 20 mm Hg below sitting pre-exercise level to a value < 90 mm Hg, occurred in 15 subjects (1.7%) with a mean age of 44.2 years. Bradycardia was associated with hypotension in only 2 subjects. When compared with age-matched controls, hypotensive subjects had higher maximal heart rates (183.9 ± 14.7 vs 173.1 ± 11.2 bpm) but no difference in SBP at submaximal or maximal effort. Post-exercise ST segment abnormalities suggestive of myocardial ischemia occurred in one third of the hypotensive subjects but none of the controls, $p < .05$.

Evaluation of Peripheral Blood Flow in Normal Man by Plethysmography

Although the incidence of degenerative changes in the blood vessels is well known to increase with advancing age, quantitative data on the changes in peripheral blood flow due to the aging process per se are lacking. Venous occlusion plethysmography has been shown to be the most accurate and reproducible method to measure peripheral arterial flow. We have used this method to evaluate peripheral blood flow in healthy subjects aged 20-83 years from the BLSA both at rest and in response to post-occlusion hyperemia, which results in near-maximal flow. Neither resting nor post-occlusion hyperemic blood flow were related to age in these 146 BLSA men and women who underwent occlusions of 1, 2, and 3 minutes both at 26°C and 35°C. These results suggest that peripheral arterial flow need not be limited by age per se in man.

In a second protocol, the response of peripheral blood flow to intravenous infusion of isoproterenol and sodium nitroprusside was determined by plethysmography in 25 healthy volunteers ages 25-84 years. The results of this study are pending.

Prognostic Significance of Specific Electrocardiographic Findings

We have previously characterized the long-term prognosis of 24 clinically healthy men with complete right bundle branch block (RBBB), identified from the BLSA population. Most recently we have characterized the clinical significance and prognosis of sinus bradycardia (SB) <50 beats/min in 47 healthy non-endurance trained men older than 40 years. When compared to a control group after a mean follow-up of 5.4 years, the SB group demonstrated a higher prevalence of associated conduction abnormalities (first degree AV block, left axis deviation and complete and incomplete RBBB) 43% versus 19%, $p < .05$. On maximal treadmill exercise testing, maximal heart rate did not differ between groups, although exercise duration was greater in the SB group, 11.0 ± 2.8 versus 9.7 ± 3.1 min, $p < .05$. None of the subjects with SB developed syncope, high degree AV block, or other manifestations of serious cardiac conduction disturbances during follow-up. Major cardiac events (angina pectoris, myocardial infarction, congestive heart failure or cardiac death) occurred in 8% of the SB group and 11% of controls over the 5.4 year mean observation period.

Effect of Age on Hemodynamic and Metabolic Exercise Performance in Normal

Man

Maximal treadmill exercise with measurement of expired gases has been performed in more than 600 clinically normal BLSA volunteers over the past 5 years. Although a formal data analysis is currently in progress, it appears that the strong age-related decline in both maximal heart rate and maximal aerobic capacity ($\dot{V}O_{2\max}$) noted in small BLSA samples will be confirmed. However, age-related changes in $\dot{V}O_{2\max}$ are attenuated markedly when $\dot{V}O_{2\max}$ is normalized for muscle mass.

To determine the role of catecholamines in the well known age-related decline in exercise capacity, we measured plasma norepinephrine (NE) and epinephrine (E) at rest and during maximal treadmill exercise in 24 healthy men. Resting NE was not age-related, but resting E was higher in men 68-77 years old than in those 22-37 or 44-55 years of age. At maximal effort both NE and E were higher in the elderly men. Furthermore, at submaximal workloads NE and E increased with age, both before and after normalization for relative effect as a percent of peak $\dot{V}O_2$. In another study, the metabolic effect of relatively prolonged aerobic exercise, is being assessed in healthy men. The relationship of $\dot{V}O_{2\max}$ to blood lipid levels and blood pressure is being determined in the entire active BLSA population via a multivariate analysis done in collaboration with the Metabolism Section, LCP.

Cardiovascular and Metabolic Performance in Highly Trained Older Men

The functional decline in cardiovascular and metabolic reserve which occurs with advancing age may not be solely attributable to biological aging but may derive in part from the increasingly sedentary lifestyle that accompanies aging. To determine the role of physical activity in preserving functional capacity, we have measured body composition, maximal aerobic capacity ($\dot{V}O_{2\max}$), cardiac

volumes at rest, during maximal bicycle exercise and lower body negative pressure, blood lipids and glucose tolerance in 19 highly trained men (T) aged 60-76 years. A comparison with 11 healthy lean sedentary controls (C) is shown below.

	T	C	P
Age	65±1	65±2	NS
% body fat	14±1	15±1	NS
VO ₂ max (ml/kg/min)	51±1	30±2	<.01
LDL cholesterol (mg/dl)	117±5	129±10	NS
HDL cholesterol (mg/dl)	59±3	49±3	<.05
Triglycerides	76±4	112±10	NS
Fasting glucose (mg/dl)	93±2	98±2	<.05
2 hr postprandial glucose (mg/dl)	104±6	124±3	<.05
Mean ± SEM			

Thus, in older men, a high level of physical activity appears to attenuate age-related declines in cardiovascular and metabolic function.

Contract N01-AG-42109, Non-invasive Assessment of Cardiac Structure and

Function in Aging Men and Women

During the past 7 1/2 years, rest and exercise thallium imaging and cardiac blood pool scans have been performed in several hundred participants of the Baltimore Longitudinal Study of Aging. This study has provided unique information concerning the effect of age on cardiac structure and function at rest and during exercise and a more accurate classification of which subjects do and do not have abnormalities in myocardial blood flow.

It is proposed that over the next 4 years cardiac blood pool scans and thallium imaging continue to be obtained in the following groups of participants for the reasons cited:

A. Gated Cardiac Blood Pool Scans

1. Repeat Scans--In 60-70 participants of both sexes, who have previously undergone this test, the scan will be repeated after beta-adrenergic blockade with propranolol. In this manner, a determination of the effect of age on beta-adrenergic modulation of cardiovascular function can be obtained. This understanding is especially important in elderly individuals since beta-blockers are among the most frequently used agents in the treatment of ischemic and hypertensive disease.

2. Scans in Patients with Latent Disease--In individuals who have no symptoms of ischemic heart disease but who nevertheless have objective reversible electrocardiographic or thallium perfusion abnormalities with stress. Numerous pathologic data indicate that the history and resting electrocardiogram correctly identify considerably less than half of the population who truly have significant coronary artery stenoses. This discrepancy becomes more marked in older individuals. Performance of exercise blood pool scans in these participants will enable us to characterize the cardiovascular function significance of asymptomatic fixed coronary disease in this large group of individuals.

3. Additional Studies in Normals--In other participants who have no evidence of ischemic heart disease by all available criteria, the very same MUGA scans ought to be made:

a. To contrast the effect of age in men with its effect in women on the cardiovascular response to stress.

b. To evaluate the effect of age on the response to other commonly employed drugs used to treat large numbers of elderly individuals, e.g. vasodilators.

c. To provide a base of 350-400 individuals for a longitudinal evaluation of the effect of age itself on cardiovascular function.

B. Thallium Perfusion Scans. Participants in the Baltimore Longitudinal Study of Aging would continue to undergo exercise thallium tests as they become eligible to do so in the next 4 years. This would include those who become 40 years of age, those who enter the program, and those who are capable of undergoing a treadmill test but who for one reason or another did not have a thallium test during the past 5 years. This would enable us to continue to identify asymptomatic reversible ischemia in the BLSA participants and allow us to better assess the accuracy of a positive test in asymptomatic individuals in predicting the future development of clinical ischemic events.

The following abstracts summarize some of the scientific progress that has evolved from this contract during FY 1986.

REDUCED EARLY DIASTOLIC FILLING RATE IN HYPERTENSIVES WITH LEFT VENTRICULAR HYPERTROPHY IS REVERSED DURING ACUTE EXERCISE AND DOES NOT LIMIT END DIASTOLIC OR STROKE VOLUME. Steven P. Schulman, Edward G. Lakatta, Walter J. Rogers, James L. Weiss, Sidney O. Gottlieb, Jerome L. Fleg, Gary Gerstenblith. Johns Hopkins Hospital and Gerontology Research Center, NIA, Baltimore, MD

Early diastolic filling abnormalities have been identified in resting hypertensive individuals with ventricular hypertrophy and are hypothesized to be responsible for compromised diastolic filling volumes and cardiac performance. We compared diastolic filling parameters and cardiac volumes at rest (R) and during upright bicycle exercise at a 50 watt workload (EX) in eight hypertensive individuals (H) (mean age = 70±5 yrs) with documented left ventricular hypertrophy (LVHT) (mean echo septal wall thickness = 14.3 ±1.3 mm) off all hypertensive therapy and ten age matched normotensive individuals (N), using gated cardiac blood pool scans (20 frames/R-R interval). All of the subjects were free from exercise thallium or wall motion abnormalities and had adequate time activity curves; those with artifact due to variations in heart rate were excluded.

	PFR	TPR	EDV	SV	CO
N-R	2.6±.6	60±4	132±26	96±19	5.2±1.3
H-R	1.9±.6*	75±7*	137±26	77±21	5.5±2.0
N-EX	4.7±1.8	78±5	144±38	107±26	10.5±2.3
H-EX	4.8±1.4	82±6	153±31	103±31	10.8±3.6

PFR = peak filling rate (EDV/sec). TPR = % of R-R interval. EDV = end diastolic volume. SV = stroke volume. CO = cardiac output. Values are mean ± S.D. * = p<.05 vs N-R.

Thus, while early diastolic filling abnormalities are present in hypertensive individuals with LVH at rest, they have no direct negative impact on SV or one of its major determinants, EDV, at rest or during EX to a load which results in

a doubling of cardiac output. Furthermore, the filling abnormalities are abolished during EX.

POSTURAL CHANGES IN CARDIAC VOLUMES IN MEN IN RELATION TO ADULT AGE. Richard J. Rodeheffer, Gary Gerstenblith, Elsie Beard, Jerome L. Fleg, Lewis C. Becker, Myron L. Weisfeldt and Edward G. Lakatta. Gerontology Research Center and Cardiology Division and Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland

Cardiac volumes by equilibrium gated cardiac blood pool scans and heart rate were measured in the supine and sitting positions in 64 male volunteer subjects (ages 25-80 yrs) who had been rigorously screened to exclude cardiovascular disease. After the assumption of upright position, the mean cardiac output of the group was unchanged but heart rate increased and stroke volume decreased due to a decrease in end diastolic volume. Neither the cardiac output in either position nor the average postural change in cardiac output, cardiac volume or heart rate was age-related. While the average cardiac output among the subjects was unaltered with a change in posture, in some individuals it increased slightly while in others it decreased. The postural change in cardiac output among the individual subjects correlated (by linear regression analysis) (1) with a change in heart rate only in younger subjects; and (2) with a change in stroke volume in all age groups, but the slope of this relationship was greater in older than in younger subjects. The postural change in stroke volume was strongly correlated with a change in end diastolic volume, and this relationship did not vary with age. Thus, the average postural change in cardiac output in an older individual depends more on a change in stroke volume and less on a heart rate change than in a younger one. This result, like the response to vigorous exercise previously demonstrated to occur with aging, indicates a greater reliance in the elderly on the Frank-Starling mechanism than on heart rate for a given change in cardiac output in response to perturbation from the basal supine state.

POTENCY OF THE FRANK STARLING RESERVE IN NORMAL MAN. D. G. Renlund, G. Gerstenblith, R. J. Rodeheffer, J. L. Fleg, E. G. Lakatta. The Johns Hopkins Medical Institutions, Baltimore, Maryland

It has recently been shown that heart rate (HR) is decreased and stroke volume (SV), end diastolic volume (EDV), and end systolic volume (ESV) are increased with no change in cardiac output (CO) in healthy aged, as compared with young, individuals during upright bicycle exercise. Is this a profile of decreased effectiveness of beta adrenergic cardiovascular modulation? To test this hypothesis and the Frank-Starling reserve (FSR) in normal man, we measured cardiac volumes via gated blood pool scans in 12 subjects aged 39-82 years without evidence of cardiac disease by history, physical exam, and stress ECG and thallium testing, during upright bicycle exercise before and after propranolol (PROP), 0.15 mg/kg i.v. Beta blockade was demonstrated by a markedly decreased sensitivity to isoproterenol-induced increase in HR (mean dose of 3.3 ug i.v. increased HR by 25 beats per minute (BPM) before and by 5 BPM after blockade, $P < .001$). Parameters during rest and exercise at 100 watts before (R1 and E1) and after (R2 and E2) PROP were:

	R1	R2	E1	E2
CO	6.4 \pm .6	6.8 \pm .6	15.5 \pm 1.5	14.8 \pm 1.7
HR	69 \pm 3	67 \pm 3	128 \pm 6	108 \pm .3***
SV	94 \pm 6	103 \pm 10	129 \pm 15	146 \pm 20*
EDV	148 \pm 12	172 \pm 18**	173 \pm 20	206 \pm 27***
ESV	55 \pm 7	69 \pm 11**	44 \pm 7	60 \pm 9***

PSP/ESV 2.9+ $\overline{.6}$ 2.3+ $\overline{.5^{***}}$ 6.2+ $\overline{1.7}$ 3.1+ $\overline{.8^{***}}$

PSP/ESV = peak systolic pressure/ESV ratio; * $p < .06$, ** $p < .05$, *** $p < .01$.

Increased EDV and SV, achieved via the FSR, maintains cardiac output during moderate exercise in the presence of beta blockade despite markedly decreased contractility and HR and increased ESV. Thus, beta blockade unmasks a very substantial FSR in normal humans during upright exercise.

LEFT VENTRICULAR FUNCTION DURING TWO SEQUENTIAL EXERCISE PERIODS SEPARATED BY ONE HOUR WITHOUT INTERVENTION. Dale G. Renlund, Edward G. Lakatta, Jerome L. Fleg, Jon F. Clulow, Gary Gerstenblith, Johns Hopkins Hospital and Gerontology Research Center, NIA, Baltimore, MD

Gated blood pool scanning can provide non-invasive assessment of cardiac volumes during exercise (EX) in the same individual before and after an acute intervention. To assess whether parameters of volume and function are comparable during two relatively closely spaced EX periods, 14 subjects, aged 33-79 (mean 55) without evidence of cardiac disease by history, exam, and stress ECG and thallium testing, underwent two maximal EX tests separated by 60 minutes. Heart rate (HR, beats/min), cardiac output (CO, L/min), stroke volume (SV, ml), end-diastolic volume (EDV, ml), and end-systolic volume (ESV, ml) were obtained at rest, at 25 watts (W), 100 W, and at the maximum workload (MAX). The difference between the two EX periods i.e. EX period 2 minus EX period 1 are (mean \pm SEM):

	REST	25 Watts	100 Watts	MAX
HR	23+2***	12+2***	10+2***	-2+4
CO	0.4 \pm	0.1 \pm 0.5	0+0.4	-0.5 \pm 0.7
SV	-16+**	-10 \pm 5	-10+3*	-5 \pm 3
EDV	-32+6***	-18+6*	-11+4*	-5 \pm 5
ESV	-17+3***	-9+3*	-2+2	0 \pm 2

(* $p < .05$; ** $p < .01$; $p < .001$)

Thus, for at least one hour following maximal EX, though CO is not changed, HR is higher and cardiac volumes are smaller at rest and at low workloads during a second EX period. With increasing levels of EX, cardiac volumes and HR converge to give identical values at MAX. The higher HR and smaller heart volumes prior to and early during the second EX period suggest that the catecholamine response associated with the first EX period persists or that volume depletion is present. Prior EX has significant effects during the early periods of subsequent EX, and caution should therefore be used in the interpretation of cardiac volume data acquired during a subsequent closely spaced EX period.

LEFT VENTRICULAR END DIASTOLIC VOLUME-END SYSTOLIC COUPLING IN MAN: A MANIFESTATION OF LAPLACE'S LAW. Dale G. Renlund, Gary Gerstenblith, Jerome L. Fleg, Edward G. Lakatta. Johns Hopkins Hospital and Gerontology Research Center, NIA, Baltimore, MD

According to LaPlace's law, the extent of ventricular fiber shortening should be inversely related to cavity size at the onset of and during contraction. This predicts a close relationship between changes in end diastolic volume (Δ EDV) and end systolic volume (Δ ESV) when systolic blood pressure (SBP) and contractility vary. To examine this relationship in man, EDV and ESV, determined by gated blood pool scans, were measured in 21 men during a postural change (POSTN) and from rest through upright bicycle exercise at a 125 watt workload (EX). The EX protocol was repeated in 31 additional volunteers following beta blockade (BB) with propranolol 0.15 mg/kg i.v. Linear regression analysis of the Δ EDV vs Δ ESV relationship among the individual subjects showed:

	m	r	p
POSTN	.49 \pm .10	.74	<.0001
0 - EX	.40 \pm .09	.71	<.0003
0 - EX with BB	.44 \pm .11	.69	<.0001

Δ ESV (cc's) ranged from -26 to +20 with POSTN, -46 to +2 with EX, and -53 to +20 with EX and BB. Δ EDV ranged from -58 to +36 with POSTN, -37 to +43 with EX and -40 to +155 with EX and BB. Δ SBP (mm Hg) ranged from -14 to +23 with POSTN, +35 to +140 with EX and +5 to +96 with EX and BB. The strong correlation between Δ EDV and Δ ESV with a remarkably similar slope indicates a tight coupling between the two during POSTN changes and with exercise which is independent of both SBP and, since it did not change after BB, inotropic state. Thus, in man, LaPlace's law is of fundamental importance in the ventricular adaptive response to POSTN and to EX.

Mechanistic Studies of Myocardial Contraction and Cell Energetics in Animal Tissues

Excitation-Contraction in Isolated Cardiac Cells

We have dissociated myocardial muscle cells from adult rats and rabbits. These preparations are being used to study the contractile, electrophysiological, and biochemical characteristics in a variety of different conditions. In particular, we have been able to identify in these isolated cells a longitudinally propagating wave which occurs spontaneously in cells with a normal resting membrane potential which are not electrically stimulated. These "waves" are likely to represent the phenomenon of spontaneous release of Ca^{2+} from the sarcoplasmic reticulum (SR) and are the cause of the scattered light intensity fluctuations (SLIF) which our laboratory has studied in the past in multicellular preparations. Our work has validated single cells as a model for the study of mechanisms of excitation-contraction coupling and in particular of spontaneous SR Ca^{2+} release. We have recently expanded our work to study the interaction between spontaneous contractile waves and stimulated twitches.

Fluctuations in the Intensity of Laser Light Scattered thru Diastolic Cardiac Muscle

We have discovered that SLIF are present in isolated rat ventricular muscle even under conditions formerly considered to be quiescent. Subsequent experiments indicated that SLIF are highly dependent on Ca^{2+} loading of the cell and could be reversibly terminated (1) by maintaining constant Ca^{2+} concentration in the myofilament space in skinned fibers; or (2) in intact fibers by caffeine. These results were interpreted to indicate that cellular myoplasmic Ca^{2+} concentration oscillates in diastole, producing motion of the myofilaments, which modulates the laser beam and results in SLIF. This myofilament motion which is asynchronous within a cell, and among cells, results in a small degree of diastolic force or "tone" in the muscle. In single myocytes, this contractile motion represents the contractile wave (vide supra). Additional experiments have demonstrated SLIF in atrial, ventricular, and conduction tissues in a range of mammalian species including man and indicate the universality of this phenomenon in excitable cardiac tissues. We have directly demonstrated these Ca^{2+} oscillations utilizing intracellular injects of the chemiluminescent protein, aequorin and modeled the effect of heterogeneous Ca^{2+} oscillation on tonic force. We have also demonstrated the presence of SLIF in the intact perfused heart and have shown that it covaries with Ca^{2+} -dependent tone. In our most recent studies, we

have determined the specific characteristics of myofilament motion that cause SLIF. We have also shown that ischemia suppresses spontaneous Ca^{2+} release and reperfusion exacerbates it.

Structure and Function of Single Cardiac Myocytes Over a Broad Age Range

There has been considerable prior work from this laboratory as well as others documenting age associated left ventricular hypertrophy. It has been deduced that the myocytes must be responsible for much of this hypertrophy, as the increase in collagen and other components of the interstitium is insufficient to account for all of the increase in mass. However, the cellular anatomic basis of age associated cardiac hypertrophy is unknown. We therefore analyzed digitized photomicrographs of isolated single left ventricular myocytes from 2, 8, and 2 month old male Wistar rats. We find that slack sarcomere length and cell width are unchanged over this age range. Cell length increases by 21%, however. Therefore, the average number of sarcomeres per cell length increases with age. This series addition of sarcomeres may have important functional implications as to the mechanism and consequences of age associated myocardial adaptation.

Excitation-Contraction Coupling in the Hyperthyroid Heart

Hyperthyroidism is known to alter both systolic and diastolic cardiac function, as well as induce left ventricular hypertrophy. To investigate the cellular basis for these phenomena, rats were rendered hyperthyroid and single left ventricular myocytes were isolated via collagenase perfusion of the intact heart. Contractile waves due to spontaneous Ca^{2+} release in the absence of stimulation as well as stimulated twitches were measured. Isolated hyperthyroid myocytes, when compared to their euthyroid controls, were found to maintain many of the contractile properties found in bulk preparation, thus validating the model and indicating that at least some of the changes in cardiac function seen in the hyperthyroid state are intrinsic to the myocardium, and not secondary to altered loading conditions or heart rate. Using contractile waves in the absence of stimulation as an indication of the frequency of spontaneous Ca^{2+} -induced Ca^{2+} release from the SR, we find that hyperthyroid myocytes have more frequent spontaneous SR Ca^{2+} release than euthyroid myocytes. Under some conditions, these waves diminish twitch amplitude to a greater extent in hyperthyroid than in euthyroid myocytes. This may provide a basis for the hyperthyroid cardiomyopathy. Hyperthyroid myocytes are also more sensitive to both the inotropic and toxic effects of digitalis glycosides than euthyroid myocytes. Glycoside augmentation of contractile waves and induction of aftercontractions seen in single myocytes may reflect the cellular basis of afterdepolarizations and aftercontractions seen in bulk muscle. Studies are in progress to analyze photomicrographs of hyperthyroid myocytes so that functional changes which we have characterized on the cellular level may be extrapolated to the level of the sarcomere, the fundamental contractile unit.

Mechanisms of Abnormal Automaticity in Cardiac Preparations

While resting mammalian ventricular myocardium does not usually exhibit pacemaker like activity, under certain conditions spontaneous localized release of Ca^{2+} from SR results in an increase in myoplasmic $[\text{Ca}^{2+}]$ (Ca_i) which causes miniature inward currents resulting in oscillations of membrane potential. At the normal resting membrane potential in cardiac myocytes this is insufficient to induce an action potential. However, when spontaneous SR Ca^{2+} release occurs

simultaneously at more than a single locus, i.e. when these loci are "synchronized," the resultant sarcolemmal depolarization is augmented to levels that are sometimes sufficient to produce a spontaneous action potential and contraction. Thus, multiple areas of localized spontaneous Ca^{2+} release within ventricular cardiac cells, if "synchronized" may provide a mechanism for abnormal automaticity in these cells and can produce a "heart beat in reverse."

Autonomic Modulation of Myocardial Cell Ca^{2+}

Ca^{2+} is a critical agent in the activation and deactivation of contraction in the heart. When Ca^{2+} binds to the myofilaments, contraction is initiated; when Ca^{2+} comes off the myofilaments, relaxation occurs. Two mechanisms have been proposed for the regulation of relaxation in cardiac tissue: (1) regulation could occur by altering the sensitivity of the myofilaments for Ca^{2+} modulating the off rate of Ca^{2+} from the contractile apparatus; or (2) Ca^{2+} could be sequestered away from the myofilament, so the Ca^{2+} necessary for contraction would no longer be available. Beta-adrenergic agonists, such as isoproterenol, both increase the off rate of Ca^{2+} from the myofilament and increase the rate of Ca^{2+} sequestration. We monitored these effects by injecting ferret papillary muscles with the photoprotein aequorin, which luminesces in the presence of free Ca^{2+} . In the presence of isoproterenol, more Ca^{2+} was needed for a given twitch force, consistent with the hypothesis that the myofilaments were less responsive to Ca^{2+} , i.e. the off rate of Ca^{2+} from the myofilaments was increased. The free Ca^{2+} concentration also fell faster in the presence of isoproterenol, implying a more rapid rate of sequestration. Isoproterenol also accelerated relaxation. The cholinergic agonist acetylcholine was also applied to papillary muscles microinjected with aequorin. For a given level of twitch force, less Ca^{2+} was required in the presence of acetylcholine than in the absence of drug, suggesting the myofilaments had become more responsive to Ca^{2+} . However, acetylcholine had no effect on relaxation. When both isoproterenol and acetylcholine were applied to the muscles, the myofilament sensitivity to Ca^{2+} was not decreased, but relaxation was accelerated. It is concluded that the modulation of relaxation by isoproterenol and acetylcholine does not occur at the level of the myofilaments.

Neurotransmitter Modulation of Cardiac Myocyte Function

The adrenergic and cholinergic components of the autonomic nervous system serve an important modulatory role in the cardiovascular system. Norepinephrine is the primary physiologic agonist in the adrenergic arm of the autonomic system. In the heart, norepinephrine is known to activate three types of receptors: alpha 1, alpha 2, and beta 1. The increase in cell Ca^{2+} by norepinephrine both augments action potential triggered sarcoplasmic reticulum (SR) Ca^{2+} release to cause an enhanced contractility and increases the likelihood for arrhythmogenic diastolic SR Ca^{2+} release, seen in myocytes as spontaneous contractile waves. While the positive inotropic effect of alpha₁-adrenergic agonists on myocardial contractility is thought to be mediated via an increase in cell inositol 1,4,5-tris phosphate (IP_3), alpha₁-adrenergic agonists also increase 1,2-diacylglycerol which activates protein kinase C. We examined the relative potency of alpha and beta mechanisms and phorbol esters on these neurotransmitter effects in single adult rat myocytes. Contractility was measured as the velocity of shortening during stimulation at 1 Hz. Waves were measured in a 30 second window following 2 minutes of stimulation. In the absence of drugs, average velocity of shortening was 70 ± 32 $\mu\text{m}/\text{sec}$ ($\bar{x} \pm \text{SEM}$, $n=6$) and no waves occurred.

Norepinephrine ($1 \times 10^{-5} M$) increased velocity of shortening to $300 \pm 70\%$ control ($n=6$), and caused 3.6 ± 1.55 waves to occur ($n=6$). Beta (norepinephrine plus prazosin ($1 \times 10^{-5} M$)) had a similar effect: velocity of shortening increased to $310 \pm 93\%$ control and 1.8 ± 0.95 waves occurred ($n=6$). In contrast, alpha (norepinephrine plus propranolol ($1 \times 10^{-6} M$)) increased velocity of shortening by $37 \pm 28\%$ ($n=6$) and no waves occurred. Thus, the increased contractility and enhanced probability for spontaneous diastolic Ca^{2+} release to occur in response to neurotransmitter release in situ are essentially beta rather than alpha in nature. In Quin2 loaded myocytes, norepinephrine and beta decreased resting Ca^{2+} and increased the rate of Ca^{2+} uptake with KCl depolarization compared to control. Alpha had no effect on resting Ca^{2+} and decreased the rate of Ca^{2+} uptake with KCl depolarization.

Role of Calcium in the Regulation of Energy Metabolism

We have continued our work on the physiological importance of Ca^{2+} ions in the regulation of energy metabolism. Specifically, we have exposed isolated cardiac myocytes to a variety of conditions expected to alter cytosolic free Ca^{2+} ion concentration and have measured the amount of the active form of pyruvate dehydrogenase (PDH_A) which results, as well as estimating Ca^{2+} concentration with fluorescent chelating agents. Protocols have included progressive plasma membrane depolarization with increasing concentrations of KCl, and the use of veratridine. Further, we have used interventions which enforce quiescence on the cells, viz. loading with chelating agents and the use of the inhibitor ryanodine, to separate the effect of Ca^{2+} on pyruvate dehydrogenase from the effects of a decrease in the ATP/ADP ratio, which is normally a sequel to increased Ca^{2+} availability in muscle. These studies have shown that Ca^{2+} is quantitatively an important signal in controlling pyruvate dehydrogenase activity in heart cells.

We have also investigated the role of Ca^{2+} in the control of pyruvate dehydrogenase in isolated hepatocytes. The hormones glucagon, vasopressin and the alpha₁ adrenergic agonist phenylephrine all led to an increase in cytosolic free Ca^{2+} concentration, an increase in PDH_A content and an increase in mitochondrial NADH content: the latter is indicative of increased mitochondrial dehydrogenase activity in general. Further, phorbol esters, which activate protein kinase C, were found to prevent increases in Ca^{2+} due to glucagon or phenylephrine, but not that due to vasopressin. In every case, there was a parallelism between effects on cytosolic free Ca^{2+} concentration and effect on PDH_A content, in strong support of the thesis that the former exercises a large degree of control over the latter.

Effect of Aging on Calcium Ion Homeostasis and Neurotransmitter Synthesis and Release

We have measured the fraction of the enzyme pyruvate dehydrogenase which exists in the active state in isolated presynaptic vesicles (synaptosomes) derived from cerebral cortex of young adult and senescent rats. This enzyme activity is crucial to the synthesis of the neurotransmitter substance acetylcholine, and is regulated by Ca^{2+} ions. Previously we have shown that the synthesis and release of acetylcholine is diminished in the synaptosomes derived from senescent animals, when compared to young adults, and others have shown a diminished entry of Ca^{2+} across the plasma membrane in response to depolarization, in senescence. This year, we studied the fraction of pyruvate dehydrogenase existing in the

active form (PDH_A) both in resting synaptosomes, and in preparations depolarized with high concentrations of KCl or with the agent veratridine. Values for PDH_A content were found to be unaffected by aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00036-06 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Interaction of Age and Physical Conditioning on Myocardium and Vasculature

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	H. A. Spurgeon	Physiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	E. S. Beard	Chemist	LCS, NIA
	M. B. Effron	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any)

Department of Dermatology, Johns Hopkins Hospital, Baltimore, MD (G. M. Bhatnagar)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

0.5

OTHER:

1.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Our laboratory has shown in many previous studies that myocardial function in rats is affected by aging, specifically by by prolonging isometric twitch duration. Biochemical correlates have been shown to change in parallel as well. We have, in previous studies, demonstrated that mild exercise which is not sufficient to induce a training effect in young animals is nonetheless able to reverse/retard cardiovascular aging when applied relatively late in the lifespan of the rat. We have subsequently attempted to define the limits of exercise in terms of type, duration, and age at which exercise is begun. The present study, utilized a swimming model begun at 5 weeks of age and continued up to 17 months of age. The contractile and biochemical parameters of the myocardium did not differ between the two groups. The absence of a training effect on heart weight or the ratio of heart weight to body weight precludes a definitive interpretation of these results. One possibility is that up to 17 months (and unlike the case for senescence) in order for physical exercise to alter myocardial properties, a training effect on heart weight or body weight must occur.

Discontinued.

IRP-LCS-139

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00038-05 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Evaluation of Peripheral Blood Flow in Normal Man by Plethysmography

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	E. S. Beard	Chemist	LCS, NIA

COOPERATING UNITS (if any)

Department of Anesthesia and Critical Care, Johns Hopkins Hospital (G. Bause)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NTA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.60

PROFESSIONAL:

.30

OTHER:

.30

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews
- ☐ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Although the incidence of degenerative changes in the blood vessels is well known to increase with advancing age, quantitative data on the changes in peripheral blood flow due to the aging process per se are lacking. Venous occlusion plethysmography has been shown to be the most accurate and reproducible method to measure peripheral arterial flow. We have used this method to evaluate peripheral blood flow in healthy subjects aged 20-83 years from the Baltimore Longitudinal Study of Aging (BLSA) both at rest and in response to post-occlusion hyperemia, which results in near-maximal flow. Neither resting nor post-occlusion hyperemic blood flow were related to age in these 146 BLSA men and women who underwent occlusions of 1, 2, and 3 minutes both at 26°C and 35°C. These results suggest that peripheral arterial flow is not limited by age per se in man.

In a second protocol, the response of peripheral blood flow to intravenous infusion of isoproterenol and sodium nitroprusside was determined by plethysmography in 25 healthy volunteers ages 25-84 years. The results of this study are pending.

IRP-LCS-141

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00029-09 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any) Division of Cardiology, Francis Scott Key Medical Center, Baltimore, MD (S. H. Gottlieb), Peter Bent Brigham Hosp., Boston, MA (T. Smith), University of Arizona, Tucson, AZ (F. Marcus), Massachusetts General Hospital, Boston, MA (R. Johnson), Duke University, Durham, NC (H. Strauss and M. Hlatky)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.1

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm.

To assess the ability of maintenance digoxin therapy to improve exercise tolerance in patients with stable CHF, systolic dysfunction and sinus rhythm, we performed maximal treadmill exercise tests in 12 such individuals while monitoring respiratory gas exchange. No difference in exercise duration, maximal oxygen consumption (VO_{2max}), maximal heart rate, or ventilation was found after 4 weeks of digoxin versus 4 weeks of placebo in a randomized crossover study. During maximal upright bicycle exercise, however, digoxin increased ejection fraction from .26 to .31 despite identical exercise tolerance.

Our group has initiated the development of a questionnaire in conjunction with experts in cardiology at different universities to sample representative groups of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. Among 2704 questionnaire respondents diuretics alone were considered the best initial therapy for CHF in 50%, digitalis alone by 8% and the combination in 33%. Two thirds of the sample felt that digitalis improved exercise tolerance. Thus, despite growing evidence that digitalis glycosides can be successfully withdrawn from patients with chronic stable CHF, there is widespread belief that these drugs are effective in most CHF patients.

IRP-LCS-144

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00035-07 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Fluctuations in the Intensity of Light Scattered thru Diastolic Cardiac Muscle

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: M. D. Stern IPA LCS, NIA

R. Weiss Medical Staff Fellow LCS, NIA

COOPERATING UNITS (if any) Cardiology Division, Dept. Medicine, Johns Hopkins Hosp., Baltimore, MD (G. Gerstenblith, D. Renlund and E. Marban), Dept. Physiology, Univ. of Maryland, Baltimore, MD (W. G. Wier), Albany Med. Ctr., Albany, NY (A. A. Kort), Dept. Pharmacology, Southwestern Medical School, Dallas, TX (J. Sutko)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.8

PROFESSIONAL:

2.7

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have discovered that scattered light intensity fluctuations (SLIF) are present in isolated rat ventricular muscle even under conditions formerly considered to be quiescent. Subsequent experiments indicated that SLIF are highly dependent on calcium loading of the cell and could be reversibly terminated (1) by maintaining constant calcium concentration in the myofilament space in skinned fibers or (2) in intact fibers by caffeine. These results were interpreted to indicate that cellular myoplasmic calcium concentration oscillates in diastole, producing motion of the myofilaments, which modulates the laser beam and results in SLIF. This myofilament motion which is asynchronous within a cell, and among cells, results in a small degree of diastolic force or "tone" in the muscle. Additional experiments have demonstrated SLIF in atrial, ventricular, and conduction tissues in a range of mammalian species including man and indicate the universality of this phenomenon in excitable cardiac tissues. We have directly demonstrated these calcium oscillations utilizing intracellular injects of the chemiluminescent protein, aequorin and modeled the effect of heterogeneous calcium oscillation on tonic force. We have also demonstrated the presence of SLIF in the intact perfused heart and have shown that it covaries with calcium-dependent tone. In our most recent studies we have determine the specific characteristics of myofilament motion that cause SLIF. We have also shown that ischemia suppresses spontaneous calcium release and reperfusion exacerbated it.

IRP-LCS-147

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00223-05 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Age on the Components of Atrioventricular Conduction in Normal Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.1

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have utilized a signal averaging, high resolution ECG to record His bundle potentials from the body surface of 111 normal Baltimore Longitudinal Study (BLS) volunteers ages 21 to 79. By allowing measurements of conduction time both proximal and distal to the bundle of His, this technique should enhance our understanding of the age-related changes in the cardiac conduction system. In 52 women, neither PR nor HV interval was related to age. In 59 men, the following age relationships were found:

PR interval = 142.4 msec + .477 age .388 <.01
PH interval = 105.3 msec + .427 age .393 <.01
PR segment = 47.6 msec + .315 age .328 <.02
Proximal PR segment = 10.5 msec + .267 age .330 <.02

Thus, an age-related prolongation of PR interval is found only in men and appears to be due largely to a delay in the proximal PR segment, presumably reflecting delay within the atrioventricular junction.

Discontinued.

IRP-LCS-152

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00033-08 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Ambulatory Electrocardiography and Blood Pressure Measurement in Normal Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

COOPERATING UNITS (if any)

Saint Louis University School of Medicine, St. Louis, MO (H. J. Kennedy)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.4

PROFESSIONAL:

0.2

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Initial ambulatory electrocardiographic data from this laboratory has characterized the normal heart rhythm patterns in healthy elderly subjects. We have extended these efforts to include younger men and women (ages 25-60). In addition, we have added a new dimension - 24 hour ambulatory blood pressure (BP) recording - simultaneous with the ambulatory ECG recording, in normal subjects as well as hypertensives and those with congestive heart failure.

We have analyzed the circadian variability of blood pressure, recorded every 7.5 min, over 24 hours in 26 healthy normotensive BLSA women ages 35-75 years using this technique. Both the mean waking systolic blood pressure (SBP) and its standard deviation increased with age whereas during sleep, the mean SBP but not its standard deviation increased with age. The difference between maximum and minimum hourly-averaged waking SBP increased with age whereas the difference during sleep was not age-related. Thus, in ambulatory, normotensive women, the variability of SBP increased with age during waking hours but not during sleep.

Discontinued.

IRP-LCS-154

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00224-05 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cardiac Myofibrillar ATPase Activity Across a Broad Age Range

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. B. Effron	Guest Researcher	LCS, NIA
Others:	G.M. Bhatnagar	Guest Researcher	LCS, NIA
	E. S. Beard	Chemist	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.5

PROFESSIONAL:

1.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

As previously reported, myofibrillar ATPase activity decreases with age while the duration of the isometric twitch in papillary muscles increases and do not appear to be related. Myosin ATPase activity and the percent of myosin isoenzyme V₁ have also been shown to decrease with age as well as with pathologic hypertrophy. Animals treated with thyroxine increased myosin ATPase activity and decreased the contraction duration and have suggested that the two parameters are related. Therefore, we treated young (2 mo), adult (8 mo), and senescent (24 mo) rats with thyroxine to produce a hyperthyroid state and were able to show that the isometric contraction time parameters decreased without altering the maximum myofibrillar ATPase activity in any group. However, when the myosin isoenzymes V₁ and V₃ were examined, a redistribution of these isoenzymes in the euthyroid state occurred with age and that was reversed by thyroxine treatment. Similarly, Ca²⁺-myosin ATPase activity in euthyroid animals showed a linear decrease with age that was only reversible in the 24 month animal where the percent of myosin isoenzyme V₁ and ATPase activity were severely depressed. Therefore, we conclude that age associated decrease in the Ca²⁺-myosin ATPase activity, myosin isoenzyme distribution, and prolongation of isometric contraction time parameters is not fixed and can be reversed with thyroxine treatment. These changes were present even though T₄ treatment caused hypertrophy of both sides of the heart. This suggests that while the myosin isoenzymes and ATPase activity may play an important role in myocardial contraction, other functions of the cell, such as sarcoplasmic reticulum Ca²⁺ sequestration, also have an important role in excitation-contraction coupling. The results also suggest that ventricular hypertrophy may be only a response, and not a cause, of alterations in myocardial biochemistry and contractile activity.

Combined into Z01 AG 00239-01 LCS.

IRP-LCS-156

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00226-04 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Excitation-Contraction in Isolated Cardiac Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. C. Capogrossi	Senior Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	D. J. Peltó	Biochem. Lab Technician	LCS, NIA
	M. D. Stern	IPA	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2

PROFESSIONAL:

0.8

OTHER:

1.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use stenderd unreduced type. Do not exceed the space provided.)

We have dissociated myocardial muscle cells from adult rats and rabbits. These preparations are being used to study the contractile, electrophysiological, and biochemical characteristics in a variety of different conditions. In particular we have been able to identify in these isolated cells a longitudinally propagating wave which occurs spontaneously in cells with a normal resting membrane potential which are not electrically stimulated. These "waves" are likely to represent the phenomenon of spontaneous release of calcium from the sarcoplasmic reticulum (SR) and are the cause of the scattered light intensity fluctuations (SLIF) which our laboratory has studied in the past in multicellular preparations. With our work we have initially validated single cells as a model for the study of mechanisms of excitation-contraction coupling and in particular of spontaneous SR calcium release. We have recently expanded our work to study the interaction between spontaneous contractile waves and stimulated twitches.

IRP-LCS-158

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00227-04 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Excitation-Contraction in Rat Myocardium: Alterations with Adult Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: C. Orchard Visiting Fellow DOD 8/31/85 LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It has been suggested that the sarcoplasmic reticulum (SR) is involved in the response of heart muscle to changes of perfusate $[Ca^{2+}]$, $[H^+]$ and stimulation rate. Two series of experiments were undertaken to investigate these suggestions. In the first, intracellular $[Ca^{2+}]$ (Ca_i) and developed tension were measured in papillary muscles from 6 and 24 month old rat hearts, during changes of perfusate $[Ca^{2+}]$ and stimulation rate. Heart muscle from the old animals, in which SR function is thought to be depressed, responded differently to changes of stimulation rate when perfusate $[Ca^{2+}]$ was high. This age-related difference was compatible with a model in which developed tension depended on Ca^{2+} cycling by the SR. In the second series of experiments, Ca_i and developed tension were measured in papillary muscles during exposure to different types of acidosis. Inhibitors of the SR were used to examine the role of the SR in the response of the muscle to acidosis. This study showed that there is an early, transient recovery of tension during acidosis which is due to increased Ca^{2+} release from the SR. Oscillations of Ca_i which are generated by the SR, and which may be important in the genesis of some types of arrhythmias, could also be produced by acidosis. Preliminary analysis of data from 6 and 24 month old rats suggests that this early recovery of tension observed during acidosis may be less than in 24 month old rats.

Discontinued.

IRP-LCS-162

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00228-03 LCS
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Complication of Maximal treadmill Exercise in Apparently Normal Subjects		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J. L. Fleg	Staff Cardiologist LCS, NIA
Others:	E. G. Lakatta	Chief LCS, NIA
COOPERATING UNITS (if any)		
LAB/BRANCH Gerontology Research Center, Laboratory of Cardiovascular Science		
SECTION Cardiac Function Section		
INSTITUTE AND LOCATION NTA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER:
1.4	1.4	
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither X <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided) <p>We have assessed the prevalence of exercise-induced ventricular tachycardia, exercise-induced supraventricular tachycardia and post-exercise hypotension in BLSA volunteers without clinical evidence of heart disease.</p> <p>Out of 925 subjects undergoing maximal treadmill exercise between September, 1977 and December 1983, 10 subjects (1.2%) developed nonsustained ventricular tachycardia (VT) during or after exercise. Episodes varied in length from 3 to 6 beats and were near associated with symptoms. The prevalence of VT was 3.8% in subjects aged 65 and older. Over a follow-up period averaging 2.0 years, no subject with exercise-induced VT developed syncope, pre-syncope, angina, myocardial infarction or sudden death.</p> <p>Exercise-induced supraventricular tachycardia (SVT) occurred in 50 subjects (5.3%). All episodes were paroxysmal atrial tachycardia; heart rate varied from 120 to 250 bpm ($\bar{x} = 175 \pm 40$). Of the 70 episodes of SVT, only 12 were ≥ 10 beats in length; 4 of these were associated with symptoms. The prevalence of SVT was 12.7% in the 245 subjects ≥ 65 years old but only 2.7% in those < 65 years. An ischemic ST segment response to exercise occurred in 14% of subjects.</p> <p>Hypotension following treadmill exercise, defined by a fall in systolic blood pressure (SBP) at least 20 mm Hg below sitting pre-exercise level to a value < 90 mm Hg, occurred in 15 subjects (1.7%) with a mean age of 44.2 years. Bradycardia was associated with hypotension in only 2 subjects. When compared with age-matched controls, hypotensive subjects had higher maximal heart rates (183.9 ± 14.7 vs 173.1 ± 11.2 bpm) but no difference in SBP at submaximal or maximal effort. Post-exercise ST segment abnormalities suggestive of myocardial ischemia occurred in one third of the hypotensive subjects but none of the controls, $p < .05$.</p>		

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00230-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Aging on Ca^{2+} Ion Homeostasis and Neurotransmitter Synthesis and Release

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI R. Hansford

Chief, EMBS

LCS, NIA

Other: F. Castro

Chemist

LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.9

PROFESSIONAL:

0.2

OTHER:

0.7

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is based upon the premise that the homeostasis of Ca^{2+} ion concentrations in neuronal tissue may be perturbed in old-age, and that this perturbation may underlie the decreased production and release of the neurotransmitter acetylcholine which has been described in old-age. We have further suggested that a decreased activation by the calcium ion of the enzyme pyruvate dehydrogenase may occur upon depolarization of nerve-terminals from aged animals, and that this may be responsible for decreased production of acetyl-CoA, and thence acetylcholine. Using rat synaptosomes (pinched-off presynaptic nerve endings from cerebral cortex) as a model, we have shown that the synthesis and release of acetylcholine as measured using radiolabelled precursors is indeed decreased in old-age. However, we have this year failed to establish any difference in the degree of activation of pyruvate dehydrogenase upon plasma-membrane depolarization when synaptosomes from 24 month old rats are compared with those from 6 month old animals. In view of the heterogeneity of synaptosomal preparations, and the strong possibility that the age-linked decrement in acetylcholine synthesis and release may only reflect the behavior of a sub-population of synaptosomes, we would regard our experimental results as preliminary results which fail to support the hypothesis outlined above, rather than as requiring the rejection of the hypothesis.

IRP-LCS-167

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00231-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Role of Calcium in the Regulation of Energy Metabolism

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R. Hansford Chief, EMBS - LCS, NIA

Others: F. Castro Chemist LCS, NIA
J. Staddon Visiting Fellow LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

2.1

PROFESSIONAL:

1.8 -

OTHER:

0.3

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

This project is designed to assess the physiological importance of calcium-ions in the regulation of energy metabolism. Specifically, we have exposed isolated cardiac myocytes to a variety of conditions expected to alter cytosolic free calcium ion concentration and have measured the amount of the active form of pyruvate dehydrogenase ([PDH_A]) which results, as well as estimating calcium concentration with fluorescent chelating agents. Protocols have included progressive plasma membrane depolarization with increasing KCl, and the use of veratridine. Further, we have used interventions which enforce quiescence on the cells, viz. loading with chelating agents and the use of the inhibitor ryanodine, to separate the effect of calcium on pyruvate dehydrogenase from the effects of a decrease in the ATP/ADP ratio, which is normally a sequel to increased calcium availability in muscle. These studies have shown that calcium is quantitatively an important signal in controlling pyruvate dehydrogenase activity in heart cells.

We have also investigated the role of calcium in the control of pyruvate dehydrogenase in isolated hepatocytes. The hormones glucagon, vasopressin and the alpha₁-adrenergic agonist phenylephrine all led to an increase in cytosolic free calcium concentration, an increase in PDH_A content and an increase in mitochondrial NADH content; the latter is indicative of increased mitochondrial dehydrogenase activity in general. Further, phorbol esters, which activate protein kinase C, were found to prevent increases in calcium due to glucagon or phenylephrine, but not that due to vasopressin. In every case, there was a parallelism between effects on cytosolic free calcium concentration and effects on PDH_A content, in strong support of the thesis that the former exercises a large degree of control over the latter.

IRP-LCS-171

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00232-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Age on Hemodynamic and Metabolic Exercise Performance in Normal Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	A. Ziemba	Visiting Fellow	LCP, NIA
	R. Andres	Chief	LCP, NIA
	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

.8.4.4

CHECK APPROPRIATE BOX(ES)

- | | | |
|--|--|--------------------------------------|
| <input checked="" type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors | | |
| <input type="checkbox"/> (a2) Interviews | | |

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Maximal treadmill exercise with measurement of expired gases has been performed in more than 600 clinically normal BLSA volunteers over the past 5 years. Although a formal data analysis is currently in progress, it appears that the strong age-related decline in both maximal heart rate and maximal aerobic capacity (VO₂max) noted in small BLSA samples will be confirmed. However, age-related changes in VO₂max are attenuated markedly when VO₂max is normalized for muscle mass.

To determine the role of catecholamines in the well known age-related decline in exercise capacity, we measured plasma norepinephrine (NE) and epinephrine (E) at rest and during maximal treadmill exercise in 24 healthy men. Resting NE was not age-related but resting E was higher in men 68-77 years old than in those 22-37 or 44-55 years of age. At maximal effort both NE and E were higher in the elderly men. Furthermore, at submaximal workloads NE and E increased with age, both before and after normalization for relative effort as a percent of peak VO₂.

In another study, the metabolic effect of relatively prolonged aerobic exercise, is being assessed in healthy men.

The relationship of VO₂max to blood lipid levels and blood pressure is being determined in the entire active BLSA population via a multivariate analysis done in collaboration with the Metabolism Section, LCP.

IRP-LCS-177

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00233-02 LCS
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Autonomic Modulation of Myocardial Cell Ca ²⁺		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)		
PI:	M. E. McIvor Others: E. G. Lakatta H. A. Spurgeon	Medical Staff Fellow Chief Physiologist LCS, NIA LCS, NIA LCS, NIA
COOPERATING UNITS (If any)		
LAB/BRANCH Gerontology Research Center, Laboratory of Cardiovascular Science		
SECTION Cardiac Function Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS: .6	PROFESSIONAL: .6	OTHER: -
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> <u>Calcium</u> is a critical agent in the activation and deactivation of <u>contraction</u> in the heart. When calcium binds to the myofilaments, contraction is initiated; when calcium comes off the myofilaments, <u>relaxation</u> occurs. Two mechanisms have been proposed for the regulation of relaxation in cardiac tissue: (1) regulation could occur by altering the sensitivity of the myofilaments for calcium, modulating the off rate of calcium from the contractile apparatus, or (2) calcium could be sequestered away from the myofilament, so the calcium necessary for contraction would no longer be available. <u>Beta-adrenergic agonists</u>, such as isoproterenol, both increase the off rate of calcium from the myofilament and increase the rate of calcium sequestration. We monitored these effects by injecting ferret papillary muscles with the <u>photoprotein aequorin</u>, which luminescences in the presence of free calcium. In the presence of isoproterenol, more calcium was needed for a given twitch force, consistent with the hypothesis that the myofilaments were less responsive to calcium, i.e. the off rate of calcium from the myofilaments was increased. The free calcium concentration also fell faster in the presence of isoproterenol, implying a more rapid rate of sequestration. Isoproterenol also accelerated relaxation. The cholinergic agonist <u>acetylcholine</u> was also applied to papillary muscles microinjected with aequorin. For a given level of twitch force, less calcium was required in the presence of acetylcholine than in the absence of drug, suggesting the myofilaments had become more responsive to calcium. However, acetylcholine had no effect on relaxation. When both isoproterenol and acetylcholine were applied to the muscles, the myofilament sensitivity to calcium was not decreased, but relaxation was accelerated. It is concluded that the modulation of relaxation by isoproterenol and acetylcholine does not occur at the level of the myofilaments. </p>		
IRP-LCS-180		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00234-01 LCS																								
PERIOD COVERED <u>October 1, 1985 to September 30, 1986</u>																										
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) <u>Neurotransmitter Modulation of Cardiac Myocyte Function</u>																										
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI:</td> <td style="width: 33%;">R. S. Danziger</td> <td style="width: 33%;">Medical Staff Fellow</td> <td style="width: 33%;">LCS, NIA</td> </tr> </table>			PI:	R. S. Danziger	Medical Staff Fellow	LCS, NIA																				
PI:	R. S. Danziger	Medical Staff Fellow	LCS, NIA																							
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Others:</td> <td style="width: 33%;">E. G. Lakatta</td> <td style="width: 33%;">Chief</td> <td style="width: 33%;">LCS, NIA</td> </tr> <tr> <td></td> <td>D. J. Pelto</td> <td>Biochem. Lab Technician</td> <td>LCS, NIA</td> </tr> <tr> <td></td> <td>M. C. Capogrossi</td> <td>Senior Staff Fellow</td> <td>LCS, NIA</td> </tr> <tr> <td></td> <td>T. Kaku</td> <td>Visiting Fellow</td> <td>DOD 5/30/86 LCS, NIA</td> </tr> <tr> <td></td> <td>C. Filburn</td> <td>Research Chemist</td> <td>LBC, NIA</td> </tr> <tr> <td></td> <td>R. G. Hansford</td> <td>Chief, EMBS</td> <td>LCS, NIA</td> </tr> </table>			Others:	E. G. Lakatta	Chief	LCS, NIA		D. J. Pelto	Biochem. Lab Technician	LCS, NIA		M. C. Capogrossi	Senior Staff Fellow	LCS, NIA		T. Kaku	Visiting Fellow	DOD 5/30/86 LCS, NIA		C. Filburn	Research Chemist	LBC, NIA		R. G. Hansford	Chief, EMBS	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA																							
	D. J. Pelto	Biochem. Lab Technician	LCS, NIA																							
	M. C. Capogrossi	Senior Staff Fellow	LCS, NIA																							
	T. Kaku	Visiting Fellow	DOD 5/30/86 LCS, NIA																							
	C. Filburn	Research Chemist	LBC, NIA																							
	R. G. Hansford	Chief, EMBS	LCS, NIA																							
COOPERATING UNITS (if any)																										
LAB/BRANCH <u>Gerontology Research Center, Laboratory of Cardiovascular Science</u>																										
SECTION <u>Cardiac Function Section</u>																										
INSTITUTE AND LOCATION <u>NIA, NIH, Baltimore, Maryland 21224</u>																										
TOTAL MAN-YEARS	PROFESSIONAL	OTHER:																								
CHECK APPROPRIATE BOXES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																										
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> The <u>adrenergic</u> and <u>cholinergic</u> components of the <u>autonomic nervous system</u> serve an important modulatory role in the cardiovascular system. <u>Norepinephrine</u> is the primary physiologic agonist in the adrenergic arm of the autonomic system. In the heart, norepinephrine is known to activate three types of receptors: alpha 1, alpha 2, and beta 1. The increase in cell calcium by norepinephrine both augments action potential triggered sarcoplasmic reticulum (SR) calcium release to cause an enhanced contractility and increases the likelihood for arrhythmogenic diastolic SR calcium release, seen in myocytes as spontaneous contractile waves. While the positive inotropic effect of alpha₁-adrenergic agonists on myocardial contractility is thought to be mediated via an increase in cell inositol 1,4,5-tris phosphate (IP₃), alpha₁-adrenergic agonists also increase 1,2-diacylglycerol which activates protein kinase C. We examined the relative potency of alpha and beta mechanisms and the effect of phorbol ester, an activator of protein kinase C, on these neurotransmitter effects in single adult rat myocytes. Contractility was measured as the velocity of shortening during stimulation at 1 Hz. Waves were measured in a 30 sec window following 2 min of stimulation. In absence of drugs average velocity of shortening was 70±32 um/sec (xSEM, n=6) and no waves occurred. Norepinephrine (1x10⁻⁵ M) increased velocity of shortening to 300±70% control (n=6), and caused 3.6±1.55 waves to occur (n=6). Beta (norepinephrine plus prazosin (1x10⁻⁶ M) had a similar effect: velocity of shortening increased to 310±93% control and 1.8±0.95 waves occurred (n=6). In contrast alpha (norepinephrine plus propranolol (1x10⁻⁶ M) increased velocity of shortening by 37±28% (n=6) and no waves occurred. Thus, the increased contractility and enhanced probability for spontaneous diastolic calcium release to occur in response to neurotransmitter release in situ are essentially beta rather than alpha in nature. In Quin2 loaded myocytes, norepinephrine and beta decreased resting calcium and increased the rate of calcium uptake with KCl depolarization compared to control. Alpha had no effect on resting calcium and decreased the rate of calcium uptake with KCl depolarization. </p>																										

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00235-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Excitation-Contraction Coupling in the Hyperthyroid Heart

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	R. Josephson	Medical Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	D. J. Peltó	Biochem. Lab Technician	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

0.9

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Hyperthyroidism is known to alter both systolic and diastolic cardiac function, as well as induce left ventricular hypertrophy. To investigate the cellular basis for these phenomena rats were rendered hyperthyroid and single left ventricular myocytes were isolated via collagenase perfusion of the intact heart. Contractile waves in the absence of stimulation as well as stimulated twitches were measured. Isolated hyperthyroid myocytes, when compared to their euthyroid controls, were found to maintain many of the contractile properties found in bulk preparation, thus validating the model and indicating that at least some of the changes in cardiac function seen in the hyperthyroid state are intrinsic to the myocardium, and not secondary to altered loading conditions or heart rate. Using contractile waves in the absence of stimulation as an indication of the frequency of spontaneous calcium-induced calcium release from the sarcoplasmic reticulum, we find that hyperthyroid myocytes have more frequent spontaneous sarcoplasmic reticulum calcium release than euthyroid myocytes. Under some conditions these waves diminish twitch amplitude to a greater extent in hyperthyroid than in euthyroid myocytes. This may provide a basis for the hyperthyroid cardiomyopathy. Hyperthyroid myocytes are also more sensitive to both the inotropic and toxic effects of digitalis glycosides than euthyroid myocytes. Glycoside augmentation of contractile waves and induction of aftercontractures seen in single myocytes may reflect the cellular basis of afterdepolarizations and aftercontractures seen in bulk muscle. Studies are in progress to analyze photomicrographs of hyperthyroid myocytes so that functional changes which we have characterized on the cellular level may be extrapolated to the level of the sarcomere, the fundamental contractile unit.

IRP-LCS-186

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00236-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Cardiovascular and Metabolic Performance in Highly Trained Older Men

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	D. Drinkwater	Visiting Fellow	LCP, NIA
	J. Busby	Medical Staff Fellow	LCP, NIA
	E. G. Lakatta	Chief	LCS, NIA
	R. Andres	Chief	LCP, NIA

COOPERATING UNITS (if any)

Johns Hopkins Medical Institutions (A. Goldberg, P. Coon, G. Gerstenblith, S. Fortney)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.3

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The functional decline in cardiovascular and metabolic reserve which occurs with advancing age may not be solely attributed to biological aging but may derive in part from the increasingly sedentary life style that accompanies aging. To determine the role of physical activity in preserving functional capacity, we have measured body composition, maximal aerobic capacity (VO_{2max}), cardiac volumes at rest, during maximal bicycle exercise and lower body negative pressure, blood lipids and glucose tolerance in 19 highly trained men (T) aged 60-76 years. A comparison with 11 healthy lean sedentary controls (C) is shown below.

	T	C	P
Age	65±1	65±2	NS
% body fat	14±1	15±1	NS
VO_{2max} (ml/kg/min)	51±1	30±2	<.01
LDL cholesterol (mg/dl)	117±5	129±10	NS
HDL cholesterol (mg/dl)	59±3	49±3	<.05
Triglycerides	76±4	112±10	NS
Fasting glucose (mg/dl)	93±2	98±2	<.05
2 hr postprandial glucose (mg/dl)	104±6	124±3	<.05
Mean ± SEM			

Thus in older men, high levels of physical activity appear to attenuate age-related declines in cardiovascular and metabolic function.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00237-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Prognostic Significance of Specific Electrocardiographic Findings

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist

LCS, NIA

COOPERATING UNITS (if any)

Cardiology Division, Medical College of Wisconsin, Milwaukee (D. D. Tresch)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

0.3

PROFESSIONAL:

0.3

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously characterized the long-term prognosis of 24 clinically healthy men with complete right bundle branch block (RBBB), identified from the BLSA population.

Most recently we have characterized the clinical significance and prognosis of sinus bradycardia (SB) <50 beats/min in 47 healthy non endurance trained men older than 40 years. When compared to a control group after a mean follow-up of 5.4 years, the SB group demonstrated a higher prevalence of associated conduction abnormalities (first degree AV block, left axis deviation and complete and incomplete RBBB) 43% versus 19%, $p < .05$. On maximal treadmill exercise testing, maximal heart rate did not differ between groups, although exercise duration was greater in the SB group, 11.0 ± 2.8 versus 9.7 ± 3.1 min, $p < .05$. None of the subjects with SB developed syncope, high degree AV block, or other manifestations of serious cardiac conduction disturbances during follow-up. Major cardiac events (angina pectoris, myocardial infarction, congestive heart failure or cardiac death) occurred in 8% of the SB group and 11% of controls over the 5.4 year mean observation period.

IRP-LCS-192

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00238-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Exercise-induced Arrhythmias in Diuretic-Treated Subjects with Hypertension

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta, Chief LCS, NIA

COOPERATING UNITS (if any)

Department of Anesthesiology, Yale University School of Medicine (G. Bause)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NTA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.4

PROFESSIONAL:

0.3

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Major controversy has recently arisen regarding a possible increased incidence of sudden cardiac death in hypertensive individuals treated with diuretics. To investigate a possible etiologic mechanism for such an outcome, we compared the prevalence and complexity of exercise-induced arrhythmias in BLSA subjects on chronic diuretic monotherapy for untreated hypertension with that in normotensive control group. Although the prevalence of exercise induced arrhythmias was higher in the diuretic treated group (D) than in controls (C) 57% versus 38%, $p < .05$, this difference was due entirely to the higher prevalence of simple ventricular ectopic beats (VEB) 44% versus 26%, $p < .05$. No difference between the groups was found in the prevalence of frequent or complex ectopic beats. Furthermore, within the D group, no difference in the occurrence of ectopic beats was found between men and women, those with resting ECG abnormalities and those without or between those with serum K < 3.7 versus those with higher serum K.

IRP-LCS-194

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00239-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Structure and Function of Single Cardiac Myocytes Over a Broad Age Range

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R. Josephson	Medical Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	R. Danziger	Medical Staff Fellow	LCS, NIA
	D. J. Peltó	Biochem. Lab Technician	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

0.9

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There has been considerable prior work from this laboratory as well as others documenting age associated left ventricular hypertrophy. It has been deduced that the myocytes must be responsible for much of this hypertrophy, as the increase in collagen and other components of the interstitium is insufficient to account for all of the increase in mass. However, the cellular anatomic basis of age associated cardiac hypertrophy is unknown. We therefore analyzed digitized photomicrographs of isolated single left ventricular myocytes from 2, 8, and 24 month old male Wistar rats. We find that slack sarcomere length and cell width are unchanged over this age range. Cell length increases by 21%, however. Therefore, the average number of sarcomeres per cell length increases with age. This series addition of sarcomeres may have important functional implications as to the mechanism and consequences of age associated myocardial adaptation.

IRP-LCS-196

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00240-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Mechanisms of Abnormal Automaticity in Cardiac Preparations

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. C. Capogrossi	Senior Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	A. Talo	Visiting Scientist	LCS, NIA
	D. J. Pelto	Biochem. Lab Technician	LCS, NIA

COOPERATING UNITS (if any)

Department of Physiology, Temple University, Philadelphia, PA (S. R. Houser and A. Bahinski)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

While resting mammalian ventricular myocardium does not usually exhibit pacemaker like activity, under certain conditions spontaneous localized release of Ca^{2+} from sarcoplasmic reticulum (SR) results in an increase in myoplasmic $[Ca^{2+}]$ (Ca_i) which causes miniature inward currents resulting in oscillations of membrane potential. At the normal resting membrane potential in cardiac myocytes this is insufficient to induce an action potential. However, when spontaneous SR Ca^{2+} release occurs simultaneously at more than a single locus, i.e. when these loci are "synchronized," the resultant sarcolemmal depolarization is augmented to levels that are sometimes sufficient to produce a spontaneous action potential and contraction. Thus, multiple areas of localized spontaneous Ca^{2+} release within ventricular cardiac cells, if "synchronized" is a mechanism for abnormal automaticity in these cells and can produce a "heart beat in reverse."

IRP-LCS-198

Annual Report of the Laboratory of Cellular & Molecular Biology

National Institute on Aging

Inorganic Biochemistry Section

The Inorganic Biochemistry Section has made considerable progress in studies on the mechanism of RNA synthesis, the importance of conformational changes in DNA, and in the development of techniques for the in vivo study of aging in humans and animals by NMR.

Active Site of RNA Polymerase. Very important results have been obtained in the study of E. coli RNA polymerase. The main purpose of this study is to determine the spatial relationships between the substrates at the initiation site (IN) and the elongation site (EL) of this enzyme. Since the function of the enzyme is to get the two substrates together in the proper spatial relationship for the formation of internucleotide bonds, the determination of this relationship addresses the mechanism of transcription, or RNA synthesis.

The substrates at IN and EL are associated with metal ions [Zn(II) and Mg(II), respectively], and an important and most difficult objective of this research is to determine the distance between these metals. Our major result this year is the measuring of this distance, which was calculated to be $5.2 \text{ \AA} \pm 0.4 \text{ \AA}$. The determination of this distance at various stages of RNA synthesis will make it possible to understand the molecular basis for RNA synthesis.

The Effect of DNA Conformation on its Ability to Act as a Template for RNA Synthesis. We have previously demonstrated that conversion of B to Z DNA leads to a dramatic decrease in the ability of DNA to act as a template for RNA synthesis. We have now shown that the B \rightarrow Z transition of poly(dGdm⁵C)·poly(dGdm⁵C) induced by either Mg(II) or Co(III) requires higher cation concentrations in the presence of RNA polymerase, in line with other experiments indicating that the enzyme prefers B DNA and destabilizes the Z-conformation. These results lead to an explanation for the fact that conversion of DNA to the Z structure, though dramatically decreasing template activity, does not completely abolish it: presumably Z has no activity, and the residual activity results from the reconversion of Z to B DNA through binding of the enzyme.

Metal Induced Conformational Transitions in DNA. The complex ion $[\text{Co}(\text{NH}_3)_6]^{3+}$ has been frequently employed to bring about the transition from B to Z DNA as a model of what is presumed to be biological mechanism for gene regulation through DNA conformational changes that reflect DNA sequences (since only certain sequences are subject to the conformational changes). This complex is effective at very low concentrations, but many metal ions are capable of inducing the transition, and we have compared some of them for their efficiency, in terms of metal concentration required to produce the effect. The ions can be placed in the following order, starting with the one that is effective at the lowest concentration:

$\text{Co(III)} > \text{Al(III)} > \text{Cu(II)} > \text{Ni(II)} = \text{Cd(II)} > \text{Zn(II)} > \text{Co(II)}$

$> \text{Mn(II)} >> \text{Ba(II)} > \text{Ca(II)} > \text{Mg(II)} > \text{Na(I)}$

As previously noted, the transition from B to Z is frequently followed by one or more subsequent transitions, and these metals differ in the types of transitions produced. Thus Zn(II), Co(II) and Cu(II) lead to an A-type structure, like Co(III). On the other hand, Al(III), Cd(II) and Ni(II) lead to a hitherto unknown conformation, which we call "W" in line with its multi-peaked CD spectrum.

In Vivo NMR Studies. We have developed a technique for the study of lung metabolism by NMR. The presence of air in the lungs causes the peaks in the NMR spectrum to be too broad, thus making metabolic studies impossible. We have obtained good ^{31}P NMR spectra of pig lungs by degassing them and perfusing with oxygenated blood. The lung preparation is stable for several hours and recovers completely from metabolic insults such as hypoxia and ischemia. A very interesting result is the lack of substantial concentrations of phosphocreatine in the lung. We have also developed a technique for chemical-shift imaging using lanthanide shift reagents. The feasibility of the technique has been demonstrated using phantoms. Potential applications of the technique to blood flow imaging and imaging of heart, kidney and other organs are being studied using animal models.

Preliminary studies indicate that 24 month old male rats from the GRC colony are more susceptible to irreversible damage than 18 month or 12-month old males, when subjected to 20 minutes of complete ischemia of the brain. PCr/Pi ratio changed dramatically during ischemia, accompanied by a drop in intracellular pH, but ATP levels were not significantly perturbed. In older animals, PCr/Pi ratio did not return to control values during reperfusion, especially after a 2nd ischemic insult.

Human Studies. A protocol for the study of changes in muscle metabolism during exercise is being presented to the BLSA Steering Committee for approval. The protocol involves isometric exercise at 20% of maximum effort for 3 min. using a hand dynamometer. Pilot studies have indicated that by collecting ^{31}P NMR spectra every 30 seconds, the rapid changes in PCr/Pi ratios can be monitored, and age-related changes in the kinetics of the metabolic processes can be assessed.

Macromolecular Chemistry Section

The work of the Macromolecular Chemistry Section continued to center on the development of methods which would make possible in vivo manipulation of the receptors for neurotransmitters in a selective and lasting manner; furthermore, significant advances were made in the development of the solubilization and administration of hormones and drugs.

Catecholamine Receptors. Diseases, in spite of the complexity of their symptoms, are caused usually by a single defect on the molecular level. Chemicals have been designed and synthesized in the Section which have the potential of creating very specific defects on the molecular level: alkylating analogs of hormones were prepared which permanently deactivate beta- and α_1 -adrenoceptors. These compounds are currently being tested for their effects on the nervous system.

Solubilizers of Lipophilic Compounds. The theoretical and experimental studies performed in the Section resulted in the design and preparation of new compounds, hydroxypropylcyclodextrins, which seem to be of great applicability. Hydroxypropylcyclodextrins were used by Dr. Thomas Carpenter from Yale University in the emergency treatment of a patient with hypervitaminosis A. Furthermore, these compounds, if a process started by the Department of Commerce succeeds, may result in new medication which would enable the supply of natural sex hormones to patients by the oral rather than the presently used injection route.

Molecular Physiology and Genetics Section

The Molecular Physiology and Genetics Section continues to elucidate the mechanisms responsible for physiological and behavioral dysfunctions of aging.

Using newly developed "hi tech" instrumentation we have further documented age related impairments in rodent learning/memory (14 unit T-maze) and sensori-motor (grip strength, tightrope, rotorod, rotodrum, exploratory activity, locomotor activity, runwheel activity, and startle response) function. Defects have been further localized in the cholinergic and dopaminergic systems by morphological and biochemical analyses. Age associated reductions in striatal dopamine receptor biosynthetic rates and cholinergic neuronal loss appear to be the most likely causes of such impairments. We continue to examine the mechanisms by which such dysfunctions can be ameliorated by dietary and neuroendocrine modulation and have begun to utilize fetal brain grafting as both a possible therapeutic strategy and research tool.

Age related impairments in calcium mobilization appear to result in the functional deterioration of many cell types, including the neurons involved in cholinergic regulation of motor function. We have utilized isolated parotid cells, a well characterized model of such generalized impairment, to further elucidate the molecular mechanisms involved. It now appears that the ability of aged cells to release calcium from intracellular stores in response to inositol triphosphate is markedly decreased. These findings are consistent with our ability to temporarily reverse age associated deficits in calcium dependent functions by the use of ionophores. Most recently we have partially restored the ability of aged pituitary cells to release gonadotropin by in vitro administration of ionophore A23187 and in vivo with 3, 4 diaminopyridine.

Changes in pituitary hormone release represent one class of altered gene expression during aging. We have been particularly interested in regulation of gene expression by steroids and have further characterized changes in the ability of receptor hormone complexes to be activated and bind to nuclear components (chromatin, nuclear matrix) during aging in various tissues. We have begun to utilize recombinant DNA probes to quantitate gene expression and dosage as a function of age in various systems. Differences in the expression of certain oncogenes have been observed in several tissues of mice with increasing age. In addition, DNA methylation patterns become altered in brain, liver and small intestines of two *Peromyscus* species during aging, proportional to their respective aging rates.

Finally, all elements are in place to initiate a pilot study on the effects of caloric reduction on the aging rate of primates at the beginning of FY 1987.

This investigation will constitute an extension of our ongoing rodent studies to examine basic mechanisms of age changes in physiological and behavioral functions and at the same time determine whether dietary restriction has beneficial effects in species higher than rodents. The latter question has become a critical one in light of the intense recent interest in the interrelationships between diet, lifespan, obesity, disease and mortality.

In summary, studies employing a wide spectrum of approaches have gained further insight into those molecular changes responsible for altered function during aging, and are seeking ways to halt, delay or reverse such deterioration.

Molecular Dynamics Section

The Molecular Dynamics Section is making important progress in understanding how cooperative interactions are transmitted between hemoglobin subunits. In addition, studies of the interaction of retinol with erythrocyte membranes suggest an important role of membrane interactions for vitamin function. A program has also been initiated to study the effect of age on rat liver microsome cytochrome P-450.

Oxygen Uptake by Hemoglobin. The effective transport of oxygen by the erythrocyte requires cooperative uptake and release of the oxygen bound to the four subunits of hemoglobin. An understanding of the long range interactions between subunits associated with these cooperative interactions has been the focal point for hemoglobin studies. The quaternary conformational change delineated by a comparison of the x-ray structures of oxyhemoglobin and deoxyhemoglobin is not adequate to explain all of the detailed experimental results on hemoglobin. We have been using electron spin resonance and Mossbauer spectroscopy to focus on protein flexibility in the ligand pocket by following the time dependent changes in the coordination of the metal center in hemoglobin at subzero temperatures. A demonstration that ligand binding transmits changes in pocket flexibility independent of quaternary conformational changes will provide a new dimension to our understanding of hemoglobin function. Our recent results indicate that the transmission of flexibility cannot only facilitate entry of ligands into the pocket but stabilizes an intermediate structure where the usual exogenous ligand and the distal histidine simultaneously interact with the heme. Such an intermediate would facilitate oxygen uptake and may provide for the new pathway necessary to explain cooperative interactions in hemoglobin.

The Interaction of Retinol with Erythrocyte Membranes. It has been proposed that the function of vitamins as well as hormones may be mediated via interactions with membranes. We have therefore performed a study to investigate the interaction of retinol with erythrocyte membranes. Although no retinol receptors have been previously identified on membranes, we have found a high affinity retinol binding site ($K_d \approx 10^8$; sites/cell = 10^6) which can be populated at physiological retinol concentrations. We have further shown that binding to this site produces a small but significant increase in membrane bilayer fluidity. The changes produced by these low concentrations of retinol would appear to involve global changes of the membrane and may be significant for retinol function.

The Effect of Age on Rat Liver Microsome Cytochrome P-450. Cytochrome P-450 plays an important role in the metabolism and solubilization of many lipid soluble substances. We were particularly interested in this system because it is a heme-protein associated with the membrane and therefore can be used to investigate how protein dynamics and function can be modulated by altering protein-lipid interactions. In collaboration with Fred Friedman of the Laboratory of Molecular Carcinogenesis, NCI, we have studied the effect of age on the testosterone hydroxylase activity of cytochrome P-450. The EPR spectra indicate changes with age in the distribution of cytochrome P-450s as well as changes produced by the binding of the testosterone substrate. We have found significant age dependent decreases in the 16α and 6β testosterone activities and surprisingly a significant increase in the 7α activity. The 7α activity increase was found by using monoclonal antibodies to coincide with an increase in the specific cytochrome P-450 with this activity. Analogous increases for 7α activity of cytochrome P-450 have been found during development.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00044-13 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Metals and Proteins on Nucleic Acid, Information Transfer and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	James J. Butzow	Commissioned Officer	IBS LCMB NIA
	Patricia Clark	Research Chemist	IBS LCMB NIA
	Yong A. Shin	Research Chemist	IBS LCMB NIA
	Peter P. Chuknyiski (EOD 5/1/86)	Natl. Res. Service Fel.	IBS LCMB NIA
	Robert E. Kilkuskie (EOD 7/1/86)	NRC Resident Research Associate	IBS LCMB NIA

COOPERATING UNITS (if any)

Laboratory of Molecular Biology, NIADDK (E. Charney, I. Levin, S. Zimmerman);
Department of Chemistry, Wichita State University (R. Singhal); Purdue University
(Arnott); Oregon State University (Johnson); University of New Mexico (Bustamanta)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging/NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

5.3

PROFESSIONAL:

4.3

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they impact on the information in such a way as to influence biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) the mechanism of involvement of aluminum in Alzheimer's disease; (3) crosslinking of nucleic acid strands by metal ions; (4) the structure of the active site of RNA polymerase; (5) metal ions and cellular aging.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00113-3 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

In Vivo NMR Studies of Aging in Cells and Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Rajasekharan P. Pillai	Visiting Associate	IBS LCMB NIA

COOPERATING UNITS (if any)

See Page 2 of this Annual Report

LAB/BRANCH

Laboratory of Cellular & Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging/NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.4

PROFESSIONAL:

1.3

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

NMR is used for the non-invasive study of aging in animals and cells, and for the study of age changes in human arms and legs. A biospec spectrometer (300/1.9) is used to study age changes in animals by multinuclear spectroscopy, using 2-dimensional NMR and saturation transfer techniques to study how metabolic rates of exchange change with age. The metabolic changes are compared to morphological changes studied by imaging techniques, which are also useful for studying changes in the distribution of drugs and metabolites. Probes designed for use with a narrow-bore Varian XL-200 spectrometer are employed to perfuse cells such as human fibroblasts of varying passage and from donors of different ages. Metabolism of the cells is studied by multinuclear NMR techniques.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00046-16 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Medicinal Chemistry Applied to Problems Prominent in Senescence

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	Josef Pitha	Section Chief	MCS LCMB NIA
Others:	John Kusiak	Research Chemist	MCS LCMB NIA
	Jan S. Milecki DOD 6-2i-86	Visiting Associate	MCS LCMB NIA
	Wieslaw Buchowiecki EOD 1-1-85	Visiting Fellow	MCS LCMB NIA
	Yasuhiro Chida EOD 4-1-86	Visiting Fellow	MCS LCMB NIA
	Takashi Ishizu DOD 4-30-86	Visiting Fellow	MCS LCMB NIA
	Lajos Szabo DOD 9-30-86	Visiting Fellow	MCS LCMB NIA

COOPERATING UNITS (if any)

Univ. of Florida, J. Hillis Miller Health Center, Gainesville, Florida; NHLBI, NIH, Bethesda, Maryland; Dept. of Neuroscience, The Johns Hopkins Univ., Baltimore, Maryland; Dept. of Pediatrics, Yale Univ., New Haven, Connecticut

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Macromolecular Chemistry Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland

TOTAL MAN-YEARS:

7

PROFESSIONAL

6

OTHER:

1

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The work on ligands for receptors of catecholamines resulted in the preparation of compounds which selectively lesion either beta-adrenoceptors or alpha one-adrenoceptors. The lesion process in question leads to irreversible deactivation of receptors located on the cell surface through alkylation with a ligand; there is no cellular death or necrosis in the tissue. The potential of the approach was demonstrated by work on the peripheral nervous system (performed within the Section) and by work on the central nervous system (performed at The Johns Hopkins University). Lesions in the periphery of rats lasted for about a week and there was no crossover into the central nervous system. Lesions in beta-adrenoceptors in the brains of rats were long lasting (>30 days) and by choice of conditions could be localized to the proximity of the injection site.

The work on solubilizers resulted in the successful experimental therapy of hypervitaminosis A by Dr. Thomas Carpenter. Also, the first steps have been initiated by the licensing office of the Department of Commerce to bring the new pharmaceutical form of sex hormones, which is based on the solubilizers developed at NIA, into practical use.

IRP-LCMB-215

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00301-3 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: I. Hormone and Neurotransmitter Action.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: G.S. Roth, Chief, Molecular Physiology and Genetic Section, LCMB, NIA

Others:

Y. Ishikawa

R. Chuknyiska

K. Kochman

J. Henry

B. Baum

M. Blackman

J. Joseph

B. Cohen

COOPERATING UNITS (if any)

Patient Care Branch, National Institute of Dental Research; Clinical Physiology Branch, NIA Armed Forces Radiobiological Research Institute; Unit of Lab. Animal Medicine, U. of Mich.

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is mainly involved in elucidating those mechanisms by which the ability of hormones and neurotransmitters to regulate physiological functions is altered during aging.

IRP-LCMB-219

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00302-3 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Physiological

Function During Aging: II. Behavioral Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: Donald K. Ingram, Research Psychologist MPGS, LCMB, NIA

Others:

M. Talan

J. Sinnott

E. Bresnahan

G. Roth

R. Cutler

E. D. London

D. Olton

D. Harrison

M. Pontecorvo

E. Bresnahan

R. Weindruch

R. Walford

Dept. Psych., J.H.U., (D. Olton); Addict. Res. Ctr. ADAMHA

COOPERATING UNITS (if any) (E. London); Dept. of Path., UCLA Med. Sch. (R. Weindruch, R. Walford); Essex Comm. Coll. (E. Bresnahan); Jackson Lab (D. Harrison); NOVA Pharm. (M. Pontecorvo); U. Rochester Sch. Med. (T. McNeil, B. Davis); F. Gage (U C San Diego, Sch. Med.); Occidental Col. (L. Hoopes)

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The purpose of this project is to assess the effects of aging at a behavioral level of analysis in animal models, to identify neurobiological mechanisms associated with these effects, and to test interventions which might alter age-related performance decrements. Rodent models are tested in a battery of sensori-motor and learning/memory tasks. Neurochemical lesions and assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, and various pharmacologic treatments. Multiple genotypes are examined to determine possible genetic involvement in the pattern of age-related behavioral impairment.

IRP-LCMB-225

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01-AG-00303-3 LCMB																					
PERIOD COVERED October 1, 1985 to September 30, 1986																							
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: III Gene Expression and the Biology of Human Longevity																							
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: Richard G. Cutler,</td> <td style="width: 33%;">Research Chemist,</td> <td style="width: 33%;">LCMB, GRC, NIA</td> </tr> <tr> <td colspan="3"><u>Other:</u></td> </tr> <tr> <td>Donald K. Ingram</td> <td>M. Talan</td> <td>B. Cohen</td> </tr> <tr> <td>J. Joseph</td> <td>G. Roth</td> <td>I. Semsei</td> </tr> <tr> <td>Shuyi Ma</td> <td>R. Setlow</td> <td>V. Wilson</td> </tr> <tr> <td>M. Simic</td> <td>C. Hames</td> <td>D. Bowden</td> </tr> <tr> <td>T. Ono</td> <td></td> <td></td> </tr> </table>			PI: Richard G. Cutler,	Research Chemist,	LCMB, GRC, NIA	<u>Other:</u>			Donald K. Ingram	M. Talan	B. Cohen	J. Joseph	G. Roth	I. Semsei	Shuyi Ma	R. Setlow	V. Wilson	M. Simic	C. Hames	D. Bowden	T. Ono		
PI: Richard G. Cutler,	Research Chemist,	LCMB, GRC, NIA																					
<u>Other:</u>																							
Donald K. Ingram	M. Talan	B. Cohen																					
J. Joseph	G. Roth	I. Semsei																					
Shuyi Ma	R. Setlow	V. Wilson																					
M. Simic	C. Hames	D. Bowden																					
T. Ono																							
COOPERATING UNITS (if any) Brookhaven National Lab. (R. Setlow); NCI, NIH (V. Wilson); National Bureau of Standards (M. Simic, D. Bergtold, M. Dizdaroglu); Evans County Heart Project (C. Hames); NIDA (E. Cone); Kyoto University (T. Ono)																							
LAB/BRANCH Gerontology Research Center																							
SECTION Molecular Physiology and Genetics Section																							
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224																							
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:																					
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																							
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> The purpose of this project is to investigate the <u>biological basis of human longevity</u>. Our major research approach has been an investigation of the <u>biochemical and molecular genetic basis</u> of the variations found in the <u>aging rate</u> observed in different mammalian species, particularly <u>primate species</u>. Specific research projects have centered on testing the <u>dysdifferentiative hypothesis of aging</u>, where molecular genetic techniques are used to determine possible age-dependent alterations in gene regulation. Recent work has been centered on <u>oncogenes</u>. The possibility that <u>active oxygen species</u> may play a role in <u>destabilizing proper gene regulation</u> has been investigated by comparative measurements of oxidative stress in mammalian species of different maximum lifespan potential. This work involves measurements of antioxidant and DNA repair enzyme concentrations. Non-invasive assays of oxidative stress are also being developed. These assays include measurement of lipid peroxides and nucleic acid base damage production in serum and urine. </p>																							

IRP-LCMB-232

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00047-16 LCMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structure-Functions Relationships in Hemoglobin and Erythrocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Joseph M. Rifkind	Chief, MDS	MDS LCMB NIA
Others:	Peter P. Chuknyiski (DOD 3/31/86)	Visiting Fellow	MDS LCMB NIA
	Periannan Kuppusamy (EOD 3/1/86)	Visiting Fellow	MDS LCMB NIA
	Abraham Levy	Visiting Associate	MDS LCMB NIA
	In Ja Rhee (DOD 8/22/86)	Guest Researcher	MDS LCMB NIA

COOPERATING UNITS (if any)

Indian Institute of Technology, Madras, India (P.T. Manoharan); Johns University School of Medicine (J. Glickson); Benedict College, SC (K. Alston); Sandia Natl. Lab., NM (J.A. Shelnut); Albert Einstein Med. Ctr., NY (J. Peisach); LMC/NCI (F. Friedman)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Molecular Dynamics Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.75

PROFESSIONAL:

3.75

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- | | | |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors | | |
| <input type="checkbox"/> (a2) Interviews | | |

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The purpose of this project is to study the mechanisms involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. The project also focuses on ways in which these functions are impaired and change with age. We have therefore studied the mechanisms involved in the oxidation of hemoglobin. Oxidation affects oxygen transport because it produces nonfunctional hemoglobin, which no longer binds oxygen. These studies have been extended to include an investigation of the stability of the entire erythrocyte and the erythrocyte membrane as well as other structure function relationships in membranes.

Annual Report of the Laboratory of Clinical Physiology

National Institute on Aging

The Laboratory of Clinical Physiology (LCP) is comprised of four sections -- Applied Physiology, Clinical Immunology, Endocrinology, and Metabolism. Research is thus by no means a comprehensive or exhaustive collation of all physiological systems. Our efforts do, however, range from the more basic aspects of physiology, including molecular genetics and cell culture, to study of aging processes in experimental animals, to investigation of physiological processes in man. The human studies rely heavily on the Baltimore Longitudinal Study of Aging (BLSA) population of men and women with supplementation by special groups of individuals with characteristics which make them especially valuable for study. Thus, selected groups of middle-aged and elderly subjects who are obese or who are remarkably physically active (master's athletes) are also under study. In addition, elderly patients who are chronically hospitalized at the Francis Scott Key Medical Center (FSKMC) provide an important group of patients for studies in research geriatric medicine. While a great deal of inter-section and inter-laboratory collaboration occurs, for convenience, the activities of the Laboratory will be reported by Section.

Applied Physiology Section

The Applied Physiology Section (APS) is concerned with studying the relationship of levels, and rates of changes in levels, of performance of physiologic and non-physiologic variables in health and disease. The two major areas are the study of bone, both osteoporosis and osteoarthritis, and a new effort on strength assessment. The latter effort was initiated because of the interrelationship of strength, and the physical stresses of muscle, on bone reabsorption and apposition. In addition, the concept of fitness has focused on aerobic conditioning (VO₂ max) and its possible relationship to metabolic and cardiovascular diseases. A similar effort is necessary to define the role of muscle strength with age on some of the functional and disease changes which occur.

Other areas of interest in the Section include ongoing studies on renal physiology, dermatoglyphics (genetics) and Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia.

Specific areas of inquiry are:

- o characterization of longitudinal changes in trabecular, and cortical bone loss in men and women and definition of the relationship of losses from the different bone types;
- o elucidation of those factors which are related to bone loss including menopause, activity, strength and nutrition;
- o definition of longitudinal changes in strength in men and women and relation to those variables which may contribute to changes (activity, nutrition, anthropometric changes) and those areas which may be affected by changes in strength (bone, movement, posture);

- o definition of longitudinal changes in osteoarthritis of the hand and relationship to disease;
- o definition of, and, elucidation of the mechanism underlying changes in renal function including glomerular filtration rates and clearance of free water; and
- o elucidation of the factors responsible for the greater loss of bone from the second metacarpal in ALS patients than in comparable immobile parkinsonism-dementia patients.

Recent research accomplishments include the following:

- o The hypothesis that high protein intake leads to a decreased kidney function was not supported by a prospective study of volunteers in the Baltimore Longitudinal Study of Aging. Protein intake, as estimated by 7 day dietary diaries was not related to simultaneous measures of kidney function (creatinine clearance) in 791 males aged 21 to 93. In the 195 subjects who had diet estimates at least 10 years (mean 13.3 yrs, range 10-18 yrs) prior to kidney function tests, there was no negative effect of higher protein intake on future kidney function.
- o Longitudinal analysis of osteoarthritis of the hand was performed on 495 BLSA male volunteers who were followed an average of 8 years. Although older subjects presented with more disease, their rate of progression was similar to that of middle age subjects. The normal (0) category progressed at a slower rate than the 1+ category; therefore, 1+ should be considered a stage of the disease rather than "questionable" and differentiated from normal.
- o Simultaneous assessments of bone mineral density by single and dual photon absorptiometry indicate that cortical bone density (radius and ulna) may be poorly correlated with trabecular bone (spine) ($R=0.56$ in females, 0.37 in males). Therefore, it is not appropriate to make inferences about bone mineral density in one part of the skeleton based on findings from another.
- o There is a defect in normal males' ability to handle a water load as manifested by lower urine flow and free water clearance, as well as a change in the time course of the response with older subjects reaching their maximums later than young individuals. This effect is not secondary to age difference in either basal levels of arginine vasopressin or in the time course or degree of suppression of AVP. It is not simply a result of the lower creatinine clearance in the elderly since, when free water clearance was expressed per unit of glomerular filtration ($Ch_{20}/C_{creatinine}$), the early time differences between young and old were still significant.

Clinical Immunology Section

The research in the Clinical Immunology Section (CIS) has been directed to the definition of immune-deficiencies of aging and to age-related disorders. The basic processes of the pathways of cellular activation are being investigated in order to gain an understanding of the mechanism of immune function. Future work will depend heavily on the investigation of gene fidelity and transcription in activated cells to help explain the defects observed in T cells from old humans in their ability to elaborate growth function and respond to activation signals.

The research objective of the Clinical Immunology Section is to study the control mechanisms in the immune response. The major effort in this regard comprises an investigation of the activation pathways in both B and T cells with the determination of activation enzymes, Ca^{++} Flux, m-RNA transcription for factors and proto oncogene products, and the types of activation signals needed for each cell type. The role of accessory cells, membrane receptors for factors, and the modulation of receptors are all important considerations in this research objective. The role of aging in these processes is assessed to determine the mechanisms of the age-related decline in immune function.

The clinical research in the Section is comprised of projects involving the BLSA volunteers and groups of individuals with various immunodeficiencies. The BLSA studies which take the bulk of the resources and personnel are directed to very basic questions in aging research. The activation of lymphocytes, the effects of cell free factors and the control of cellular function are the main points in this research. The findings are that there are several pathways for cellular activation and depending on the type and concentration of the activation signal, the cell will develop along different pathways. The connection between membrane receptor and nuclear events is of main concern. The transcription of genes for factor synthesis and membrane receptors is being studied extensively. To date the findings suggest a defect in cells from the elderly in the transcription of these genes with the resulting deficit in membrane receptor expression, factor synthesis, proliferation, and function in an immune response.

Recent research highlights include:

- o T Cell Activation: Using a monoclonal antibody against the CD-3 epitope on T cells, it is possible to obtain a "physiologic" activation event since CD-3 is the T cell antigen receptor. A clearer picture has been seen in the age related decline of T cell activation than obtained using the mitogen activation system which activated CD-2 and CD-3 receptors. The T cells from older people express less IL-2 receptor and secrete less IL-2 than do cells from young people. It can also be shown that m-RNA transcription for IL-2R and IL-2 is less in the cells from old people and is dependent on the types and concentrations of the activating agents.

- o EBV Infections: Infection with Epstein-Barr Virus is an ubiquitous event as evidenced by the serum antibody level in individuals. However, in analyzing oral secretions for EBV using a c-DNA probe, it was found that a subgroup of elderly individuals secrete virus which indicates an active chronic EBV infection. The clinical significance of this infection is being analyzed.
- o Clostridium Difficile Infection in a Nursing Home Population: After an outbreak of C. difficile infection in a chronic care facility, it was found that about 1/3 of the residents carried the organism in their intestinal tract. It was not able to be erradicated by therapy and was spread to other patients by nosocomial transfer and by the introduction of new carriers into the facility. The organism is not routinely screened for, is an important pathogen, and may be endemic in nursing home populations.
- o IL-2 Effects on B-Cells: Although B cells do not express IL-2 membrane receptors, there are IL-2 mediated changes able to be seen. IL-2 can augment ongoing proliferation of B-lymphoblast lines, augment IgM secretion by these lines and, in some lines, IL-2 can induce IgG secretion. These functional changes are accompanied by changes in membrane expression of Ig, DR, and Leu-12 antigens. Therefore, IL-2 can influence proliferating B-cells in the absence of T-cells.
- o Lymphocyte Counts and Subsequent Mortality: The numbers of lymphocytes in the blood was found to decline in the period 3 years prior to death. This was not an age related phenomenon. The mechanism of this change is being investigated.

Endocrinology Section

The Endocrinology Section (ES) is engaged in a variety of projects that are directed to the goal of better understanding the biochemical and physiologic basis of age-related alterations of hormone secretion and action. The studies involve intact human subjects, animal models, tissue and cell culture techniques, and cell-free systems.

Because they can be isolated in pure form and show well defined age-related change of hormone responsiveness, fat cells isolated from animals and man offer unique advantages for studies of the biochemical endocrinology of aging. We have examined the precursor cells (preadipocytes) from adipose tissue that mature into fat cells and found them to exhibit striking differences from those of fat cells obtained from animals. Thus, we could not examine the question: Would the age of the animal program the developing and differentiating preadipocytes to exhibit the same type of change in vitro as is seen with cells isolated directly from adipose tissue?

Because of these results with preadipocytes, we have attempted to obtain cells which are derived from mature adipocytes. We are now able to culture such cells from what are usually thought of as post-mitotic cells. We have termed these cells "postadipocytes." They are morphologically different from preadipocytes, and their biochemical characteristics are under intense study. beta-receptors and the adenylate cyclase system develop quite readily. These cells do appear to show biochemical characteristics of the beta-adrenergic system more like those of adipocytes, but they have acquired hormone responsiveness to prostaglandins, i.e., the cells have undergone some degree of dedifferentiation. Recent work elsewhere using 3T3 preadipocytes, a tumor cell line, indicates that the interaction of the growth factor IGF-1 (somatomedin C) and growth hormone are critical for terminal differentiation. Such experiments will soon be undertaken with both post-adipocytes and preadipocytes in an attempt to determine whether the biochemical characteristics of these cells under conditions of culture are intrinsic or the result of environmental factors in vitro.

The biochemistry of preadipocytes has been further studied to elucidate the mechanism that determines the presence of stimulatory or inhibitory response to prostaglandins. The determining factor may be a decreased amount of the inhibitory regulatory protein N_i . It would appear that in the absence of sufficient N_i having developed, prostaglandin can act only through the dominant N_s pathway. The same decrease may account for the impairment of catecholamine responsiveness, since a proper ratio of N_i/N_s appears necessary for a stimulatory response to catecholamines.

Studies of the regulation of beta-adrenergic binding to receptors have continued. The proposed general notion that guanine nucleotide regulation of beta-receptor affinity is altered during aging has not been confirmed in our laboratory. Thus, our work with tissues from rat heart and lung suggests that the changes reported by others may be due to methodologic or environmental (nutritional?) influences that allow an effect of aging to be exhibited, but that the nature of that determinant is presently obscure.

The regulation of the numbers of beta-receptors in rat pineal during light and dark exposure is lost with maturation rather than during senescence, as has been reported, and is another example of the need to compare changes across the life span. A complicated pattern of changes of beta-endorphin and dynorphin-17 have been seen in the pituitaries and hypothalami of rats. The results suggest that aging is accompanied by changes of endogenous opioid peptides.

A mitogenic factor for fat cell precursors (preadipocytes) is present in rat serum. Results to date suggest that the factor differs from others that have been described. We have established a quantitative bioassay using primary cell culture or cloned preadipocytes. The substance is a heat labile, nondialyzable material. Determination of molecular weight and other biochemical properties are in progress.

Isolated rat anterior pituitary cells from old vs. mature male and female rats are studied in vitro. Production of TSH, prolactin, and gonadotropins (LH and

FSH) are studied after treatment with specific stimulatory and inhibitory compounds including TRH, LHRH, estrogen, dopamine, and iontophores. Altered in vitro function of pituitary cells from old rats has been found, corresponding to the alterations in circulating levels and secretory responsiveness of the same pituitary hormones observed in vivo in old animals. Pretreatment of old and young rats for up to 24 hours with pulsatile doses of LHRH does not restore function of cells derived from old rats to levels observed from cells of younger animals. Similarly, enhanced transmembrane transport of calcium ion with iontophore A23187 does not reverse the age-related defect in LH secretion, suggesting that at least part of this decrease is due to altered cell function distal to the point in the secretory pathway at which calcium acts. These data support our prior results suggesting an intrinsic age-related derangement in pituitary gonadotropic function. We have also described enhanced basal and estrogen stimulated Prl secretion by pituitary cells from old female rats, an increase in function disproportionate to the smaller increase in lactotrope number in aging rat pituitary glands. In contrast, we have found decreased basal and modulated Prl secretion by pituitary cells from old male rats. A new research direction undertaken this year involves investigation of the role of oxygen free radicals in the phenomenon of "in vitro" aging of Leydig (testosterone-secreting) cells. Preliminary experiments have demonstrated isolated Leydig cells from both mature and old male rats to have lower activity of the protective enzyme, copper-zinc superoxide dismutase, than cells derived from seminiferous tubules, which normally surround (and may protect) Leydig cells from superoxide damage in vivo.

Clinical studies underway or recently completed gather data on pituitary secretory function as it relates to gonadal, thyroid, adrenal, and growth hormone regulation in normal aging humans. We have now completed initial studies in healthy men in the Baltimore Longitudinal Study of Aging addressing hypothalamic releasing factor responsiveness of each of the major anterior pituitary hormone axes. In order to determine the relative effects of aging vs. disease on male reproductive function, we have measured testosterone, testosterone binding, and gonadotropins in a large group of men of various ages with and without chronic illness, and have found that there is a subtle, but highly significant decrease in both total and free plasma testosterone (T) with age which is accompanied by an increase in FSH, but not LH. The effects of illness on sex steroids, however, are far more profound than are the effects of aging, with lower free (but not total) T in patients with benign disease, and lower free and total T in patients with cancer. Continuing studies address the interrelationships among circulating estrogens and androgens, incidence or cardiovascular disease, and known cardiovascular risk factors, such as lipoprotein profile, obesity, and body fat distribution. Finally, we plan studies of the temporal regulation and feedback sensitivity of the ACTH-adrenal axis in the coming year.

Metabolism Section

The underlying objective of the Metabolism Section (MS) is to gain an understanding of the metabolic complexities associated with aging. In the simplest terms, "primary" biological processes of aging are associated with a wide variety of "secondary" processes. The latter processes include such

variables as inactivity, diet, body composition changes (lean body mass, obesity, and fat distribution pattern), and the effects of multiple disease processes and medications. On the one hand, it is our objective to dissect away the secondary effects so that true biological aging processes in man can be understood. On the other hand, the secondary processes may well prove to be of equal or greater importance in the determination of the overall picture of the aging human being. An understanding of these effects and of their relationship to primary aging processes is fundamental for the planning of rational processes to maintain health during aging and to prevent the diseases and infirmities so characteristic of the elderly.

Specifically, the research objectives of the Metabolism Section are: (1) to describe age differences and age changes in metabolic variables; (2) to determine biological mechanisms underlying those age effects; (3) to assess the impact of those age effects on other variables, on disease development, and on mortality; and (4) to define normative standards as influenced by age. The major metabolic variables include glucose homeostatic factors, insulin secretion and sensitivity to insulin, body composition including lean body mass, obesity, and fat distribution, acute effects of physical activity, long-term effects of physical fitness, and dietary variables, serum lipids, and adipose tissue metabolism.

Recent accomplishments include:

- o In order to understand the factors which determine the distribution of fat in the body (as measured by the waist:hip ratio), the metabolic responsiveness of subcutaneous adipose tissue from the abdominal and buttocks areas to hormonal (adrenergic) stimulation was measured. The breakdown of fat inside the adipose tissue cell (lipolysis) so that it can be released into the blood stream is under both stimulatory (beta) and inhibitory control (alpha). It was found that in men with a dangerous pattern of fat distribution (a high waist:hip ratio) there is an excessive inhibitory or alpha effect so that it is more difficult for them to reduce the amount of abdominal fat.
- o Important evidence on the mechanism underlying some of the benefits of physical activity came from an analysis of the relation of maximal aerobic capacity ($\dot{V}O_2$ max), the prime measure of physical fitness, to coronary risk factors (glucose tolerance, serum lipids, and blood pressure). The question addressed was whether fitness had effects independent of its correlations with age, obesity, and fat distribution pattern (waist:hip ratio). In both men and women who ranged from the early adult to the late years of life, fitness was generally not an important independent predictor of benefit. The favorable associations of fitness with coronary risk factors seem to act through their effects on body composition. These results confirm studies on "habitual physical activity level" in the BLSA population, that is, the overall caloric expenditure level as determined by an activity questionnaire.

- o Understanding of age changes in glucose tolerance in women has been hindered by the additional complexities of the possible endocrine-metabolic effects of (1) phase of the menstrual cycle, (2) use of oral contraceptive agents in the pre-menopausal years, (3) "passing through" the perimenopausal years, (4) use of estrogen in the post-menopausal years, and (5) hysterectomy. An analysis of a very carefully screened group showed a large progressive decline in glucose tolerance over the adult age span. Of the factors above, only oral contraceptive agents and estrogen had effects on tolerance, the first being associated with poorer results, the latter with improved tolerance.
- o The level of physical fitness is the primary determinant of the basal serum testosterone levels in the BLSA men. Testosterone concentrations invariably increased on a prolonged (one hour) intensive treadmill exercise test. The increase was lower in older men and in obese men, but in a multiple regression analysis, it was the fitness level of the men (the $\dot{V}O_2$ max) that determined the testosterone response; age and obesity did not significantly contribute independently to this association.
- o Longitudinal analysis of the effects of changes in body weight in the BLSA men and women showed that, on the average, when men lost weight they tended to lose fat almost equally from the abdominal and buttocks areas while women had much greater loss of fat from the abdominal area. Thus the waist:hip ratio, an important predictor for coronary disease risk factors, was little changed in men but was very favorably influenced in women. There are men with a "gynoid" pattern of change with weight loss and women with an "android" pattern. It will be important to follow these individuals to determine whether these characteristics influence outcomes such as development of coronary disease and overall mortality.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00021-23 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Study of Normal Human Variability		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between; margin-top: 10px;"> C.C. Plato Sr. Research Geneticist LCP NIA </div>		
COOPERATING UNITS (if any) See attached page.		
LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology		
SECTION Applied Physiology Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS: 0.40	PROFESSIONAL: 0.10	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <div> <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews </div> <div> <input type="checkbox"/> (b) Human tissues </div> <div> <input type="checkbox"/> (c) Neither </div> </div>		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) <p style="margin-top: 10px;"> This project represents an ongoing collaborative effort, involving WHO and other national and international laboratories to coordinate the collection, evaluation and interpretation of <u>normal genetic markers</u>. Specifically, the objectives of this project are: (A) To study the distribution of Dermatoglyphic markers in aging related disease entities and normal control samples, and to utilize these genetic markers in understanding the etiology, development and early diagnosis of diseases or processes with late onset. (B) To determine the <u>lateral functional dominance</u>, <u>grip strength</u>, among BLSA participants, and assess their relationship to physiological processes or diseases demonstrating <u>bilateral asymmetry</u>. </p>		

IRP-LCP-253

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00022-10 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Investigations of Bone Mineral Density and Bone Loss		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> C.C. Plato Sr. Research Geneticist LCP NIA </div>		
COOPERATING UNITS (if any) Laboratory of Central Nervous System Studies, NINCDS		
LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology		
SECTION Applied Physiology Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS: <div style="display: flex; justify-content: space-between;"> 2.1 0.70 1.4 </div>	PROFESSIONAL: 	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> Bone loss together with osteoarthritis (see project Z01 AG 00290-01 LCP entitled "Osteoarthritis and Aging") is one of the two principal age related changes of the human skeleton. Even though these changes are considered universal phenomena inherent to aging, they may result in incapacitating ailments. Advanced bone loss may result in <u>osteoporosis</u> and frequent <u>bone fractures</u>. At some time during the fourth decade of life, the human skeleton begins to lose bone. That is, bone mass decreases in relation to bone volume. In tabular bones, bone is resorbed from the endosteal surface. Because of the thinning of the cortical bone shell, bones lose their mechanical integrity and fracture more readily. The trabecular bone mass of the vertebral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and are more vulnerable to vertebral collapse. Vertebral compression fractures and fractures of the femoral neck are the most serious consequences of bone loss. The following skeletal sites are involved in the present study: <u>hand-wrist</u>, <u>ulna</u> and <u>radius</u> and <u>vertebral column</u>. This project deals with the epidemiological, genetic and longitudinal aspects of bone loss (1) among the participants of the Baltimore Longitudinal Study, (2) in a sample of normal adult Guamanians (Chamorro), (3) among patients afflicted with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam, (4) to ascertain bone mineral differences between long distance runners (running at least 40 miles daily) and relatively inactive normal controls, and (5) study of bone mineral density and effect of muscular activity on bone in rats. </p>		
IRP-LCP-258		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00028-10 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Epidemiological & Genetic Studies of ALS/PD Complex of Guam		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> C.C. Plato Sr. Research Geneticist LCP NIA </div>		
COOPERATING UNITS (if any) C & F Research, NINCDS		
LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology		
SECTION Applied Physiology Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS: <div style="text-align: center;">0.40</div>	PROFESSIONAL: <div style="text-align: center;">0.10</div>	OTHER: <div style="text-align: center;">0.30</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews </div> <div> <input type="checkbox"/> (b) Human tissues </div> <div> <input type="checkbox"/> (c) Neither </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>In an effort to elucidate the etiology of high incidence of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) on the island of Guam, a patient-control prospective study (Registry) was established in 1958. The Registry includes, in addition to the patients and their individually matched controls, their respective parents, sibs, offspring and spouses. The objective of the registry has been to determine (1) whether relatives of ALS and PD patients have higher risk for developing the disease than relatives of controls and (2) if familial occurrence does exist, to determine the extent of genetic involvement in the etiology of the disease. A twenty-five year follow-up analysis of the registry has just been concluded and the results are published.</p> <p>Other objectives of this study are: 1) to investigate the <u>genetic and epidemiological factors</u> contributing to the very high incidence of <u>Amyotrophic Lateral Sclerosis</u> and <u>Parkinsonism Dementia (ALS/PD)</u> on Guam; 2) to evaluate the distribution of the various established <u>genetic and anthropological markers</u> among the normal Guamanian population and compare them with those of the ALS/PD patients; and 3) to ascertain the effects of <u>immobilization</u> due to <u>paralysis on bone density</u>.</p>		
IRP-LCP-264		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00290-01 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <u>Osteoarthritis and Aging</u>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> M.J. Busby Medical Staff Fellow LCP NIA </div>		
COOPERATING UNITS (if any) <div style="text-align: center;"> Rheumatology, Francis Scott Key Medical Ctr. Laboratory of Personality & Cognition, NIA </div>		
LAB/BRANCH <div style="text-align: center;">Gerontology Research Center, Laboratory of Clinical Physiology</div>		
SECTION <div style="text-align: center;">Applied Physiology Section</div>		
INSTITUTE AND LOCATION <div style="text-align: center;">NIA, NIH, Baltimore, Maryland 21224</div>		
TOTAL MAN-YEARS <div style="text-align: center;">1.3</div>	PROFESSIONAL <div style="text-align: center;">0.7</div>	OTHER <div style="text-align: center;">0.6</div>
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews </div> <div> <input type="checkbox"/> (b) Human tissues </div> <div> <input type="checkbox"/> (c) Neither </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>The most common rheumatic disease of the elderly is osteoarthritis. Forty million Americans are estimated to have radiological evidence of osteoarthritis; the majority are asymptomatic. Progressive increases in both numbers of persons involved and extent of osteoarthritic changes are known to occur with aging. However, it is not clear whether the rate of progression is the same in young, middleaged, and older persons. Similarly, the rate of development of osteoarthritis is not well defined. A controversy also exists regarding exactly where on the established scale of measurement for radiographic changes (0 to 4+, with 2+ considered to be definite disease) osteoarthritis actually begins. Cross-sectional studies provide valuable prevalence or correlative data and are important in determining the relationship between radiographic disease, symptoms, treatment, and functional status. Longitudinal studies provide the insight into the natural history and long progression of aging and disease states.</p> <p>This project is both a longitudinal study designed to determine the progression of osteoarthritis by evaluation of radiographic changes on hand X-rays and a correlative study to examine the interrelationship of symptoms, physical exams, and X-rays in several joints.</p>		
IRP-LCP-267		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00291-01 LCP

PERIOD COVERED October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physiology of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Jordan D. Tobin Chief, Applied Physiology Section LCP NIA

COOPERATING UNITS (if any)

Metabolism Section, NIA, NIH
Cognition Section, NIA, NIH

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2.4

PROFESSIONAL:

1.4

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies of age changes in physiologic systems have focused on the renal system of male volunteers of the Baltimore Longitudinal Study of Aging (BLSA). The possible effect of diet, specifically protein intake, on present and future kidney function (creatinine clearance) was examined. Dietary protein has an insignificant effect on simultaneous clearances or on renal function 10-18 years after the diet estimation when studied across the entire age range, and the profound effect of age is taken into account. In separate age groups, there is a small but significant positive correlation of increasing protein and increasing creatinine clearance measured at the same time, but no negative effect of higher protein intake on future clearance. In this normal population, there is no evidence to support the hypothesis that increased protein intake leads to decreased renal function.

Water load tests on normal males of the BLSA demonstrated a marked defect in the ability of older subjects to excrete water. This was manifested by lower free water clearance and lower maximum urineflow in the elderly, as well as a change in time course of the response with older subjects reaching their maximum values later than the young.

Studies on the glucose tolerance tests in female volunteers of the BLSA and clamp studies on athletes and volunteers from the teaching nursing home populations are reported in the Metabolism Section reports.

Studies on the relationship of diabetes to cognitive function are presented in the Cognition Section reports.

IRP-LCP-270

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00093-14-LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Basis of Regulation of the Humoral Immune Response

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: A. A. Nordin Research Chemist LCP, NIA

Others: J. J. Proust Visiting Associate LCP, NIA
G. D. Collins Biologist LCP, NIA
M. A. Buchholz Biologist LCP, NIA
R. K. Chopra Visiting Fellow LCP, NIA
F. J. Chrest Biologist LCP, NIA

COOPERATING UNITS (if any)

C. Filburn, LBC, NIA, D. Kittur, Dept. Surgery, Johns Hopkins University, Baltimore, MD 21221

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore Maryland 21224

TOTAL MAN-YEARS:

4.2

PROFESSIONAL:

2.8

OTHER:

1.4

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies were carried out to determine if the hydrolysis of phosphatidyl-inositol 4,5 bisphosphate (PIP₂) is involved in transmitting an external stimulus into internal signals that result in the activation of B and T lymphocytes. Polyclonal activating agents (PAA) as well as lymphokines were used alone or in various combinations as agonist. Murine G₀ B cells induced by various PAA express IL-2 receptors when both translocation of protein kinase C and an increase in intracellular calcium ([Ca⁺⁺]_i) resulted from the activation process. However, B-cell proliferation induced by PAA did not require the expression of IL-2 receptors nor the hydrolysis of PIP₂.

Purified murine G₀ T-cells do not proliferate when cultured with phorbol myristate acetate (PMA) or calcium ionophores but actively proliferate when both substances were present in optimal amounts. PMA, but not ionophores, when combined with exogenous IL-2 induced the proliferation of G₀ T-cells. Neither PMA nor ionophore stimulation resulted in detectable levels of IL-2 but when added together to G₀ T-cells significant amounts of IL-2 were produced. Con A stimulation of G₀ T-cells resulted in translocation of PK-c and an increase in [Ca⁺⁺]_i. These data suggest that activation of PK-c is an essential event in the expression of IL-2 receptors and that IL-2 production requires in addition an increase in intracellular CA⁺⁺. T-cells from both humans and mice of different age show a reduced translocation of PK-c with advancing age which suggests a molecular basis for an age associated decline in T-cell function.

IRP-LCP-274

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00095-13-LCP

PERIOD COVERED

October 1, 1985 - September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Role of Cell Membrane Structures on Cellular Recognition

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA
Others:	J. E. Nagel	Medical Officer, PHS	LCP, NIA
	R. K. Chopra	Visiting Fellow	LCP, NIA
	B. S. Bender	Medical Staff Fellow	LCP, NIA left 6/86
	F. J. Chrest	Biologist	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA
	W. O. Boto	NRC Fellow	LCP, NIA EOD 3/86

COOPERATING UNITS (if any)

Dr. R. Winchurch and Dr. S. Huang - Dept. of Surgery, Dr. M. Liu, Dept. of Medicine, FSK Medical Center, Johns Hopkins Univ., Balto., MD 21224
Dr. A. Piirsoo - IREX Fellow

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

3.8

PROFESSIONAL:

2.1

OTHER:

1.7

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Investigation of immunodeficiencies in AIDS patients, burn patients, renal dialysis patients and infections in nursing home residents, along with basic studies on cellular recognition by mouse T cells and pulmonary lavage cells has resulted in the following insights. Macrophage/monocyte recognition of antigen proceeds through Fc receptor binding of specific antibody. The function can be boosted by interferon and is deficient in patients with AIDS. Burn patients have endotoxemia induced NK cell functional abnormalities. Dialysis patients have evidence of chronic viral infections, especially if they have been transfused. T cell recognition of alloantigen requires the participation of the target cell in initiating the activation of the T cell.

IRP-LCP-278

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00096-13-LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Low Temperature Effects on Cells of Aging Individuals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. A. Brock	Research Biologist	LCP, NIA
Others:	W. H. Adler	Medical Officer, PHS	LCP, NIA
	R. S. Pyle	Bio. Lab. Tech.	LCP, NIA

COOPERATING UNITS (if any)

H.J. Hoffman, D. W. Denman III, Biometry Branch, NICHD

LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

1.1

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

Splenic lymphocytes from young, 15 month old and 24-28 month old C57BL/6 mice housed in a constant environment were studied. Single cell suspensions were cultured in vitro with T cell mitogens, phytohaemagglutinin and Concanavalin A, and the B cell mitogen, lipopolysaccharide. Functional capacity of the T and B lymphocytes was assessed by the mitogen-induced incorporation of tritiated thymidine by dividing cells.

Age-related changes in the properties of circannual rhythms expressed by T and B lymphocytes following activation by mitogens in vitro were described previously and more critical evaluations of some parameters have been made. Phase reference points calculated for each data series showed increases in free-running periods of cells stimulated with Concanavalin A from 371 days for young mice to 458 days and 455 days for 15-month old and senescent mice, respectively. Similar increases with age in periods by an average of 55 days and 168 days for cells activated with phytohemagglutinin and lipopolysaccharide were found. Power spectral analysis of each data series and analyses for coherence between pairs of series provided independent, objective evidence for similar low frequency rhythms (longer than 52 weeks) in all data series. These changes in periodicity in addition to decreased amplitudes of T but not B cell rhythms in cells from senescent mice result in another example of imbalance in the immune system with age.

The degree of stress induced by cryopreservation of lymphocytes from young mice changed seasonally and was maximal during the months that activation of unfrozen cells was minimal. During the fall and winter, decreased percentages of viable cells were recovered, greater numbers of cells lysed, and mitogenic stimulation in vitro resulted in reduced incorporation of tritiated thymidine. These seasonal patterns of change in cryopreservation properties resembled and reinforced the circannual rhythmicity in functions of unfrozen lymphocytes.

IRP-LCP-283

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00104-10-LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Immune Survey of the Longitudinal Project Participants*

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: W. H. Adler Medical Officer LCP, NIA

Others: +J. J. Proust Visiting Associate LCP, NIA
J. E. Nagel Medical Officer LCP, NIA
B. S. Bender Medical Staff Fellow LCP, NIA left 6/86
F. J. Chrest Biologist LCP, NIA
R. S. Pyle Bio. Lab Tech. LCP, NIA

COOPERATING UNITS (if any)

Dr. M. Liu, Department of Medicine, Johns Hopkins University, Francis Scott Key
Medical Center, 4940 Eastern Avenue, Baltimore, MD 21224

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

3.05

PROFESSIONAL:

2.25

OTHER:

.8

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

These studies collect information on the immune function of participants in the Baltimore Longitudinal Study of aging to determine age-associated changes, and to relate these changes to clinical disease. A secondary goal is to evaluate the ability of existing assays of immune function to provide a meaningful and accurate assessment of immune competence and to develop new methods and assays to evaluate host immune function.

Others: +B. A. Dorsey Bio. Lab Tech. LCP, NIA
W. M. Boto NRC Fellow LCP, NIA EOD 3/86
R. Chopra Visiting Fellow LCP, NIA

IRP-LCP-286

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00011-13 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Hormones and Aging. I. Adenylate Cyclase and Hormone Action		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.I. Gregerman, M.D., Chief, Endocrinology Section, Clinical Physiology Branch, (Unit I) National Institute on Aging		
COOPERATING UNITS (if any) Department of Surgery, Francis Scott Key Medical Center Department of Medicine, Endocrinology Division, University of Melbourne, Australia		
LAB/BRANCH Gerontology Research Center, Clinical Physiology Branch		
SECTION Endocrinology Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The project includes studies on the biochemistry of <u>hormone-sensitive adenylate cyclase</u> in a variety of tissues. Their purpose is to explore the mechanisms by which age produces alterations of hormone-responsiveness in biological membranes, with special emphasis on the relationship between adenylate cyclase and <u>hormone receptors</u> . Aging in <u>fat cells</u> is being studied in tissue culture of <u>preadipocytes</u> and dedifferentiated mature fat cells (<u>postadipocytes</u>) from rats.		

IRP-LCP-291

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00013-11 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones, Hormone Receptors, and Aging. III. Aging and Human Endocrine Regulation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, Clinical Physiology Branch, NIA
(Unit II)

COOPERATING UNITS (if any)

Developmental Endocrinology Branch, NICHD. NIH
Department of Medicine, Francis Scott Key Medical Center
Cardiology Section and Metabolism Section, LCP, GRC

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Endocrinology Section and Human Performance Sections

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.6

PROFESSIONAL:

1.4

OTHER:

0.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Our clinical studies gather data on pituitary secretory function as it relates to gonadal, adrenal, thyroid, prolactin, and growth hormone regulation in normal aging humans. Our most recent findings were that growth hormone (GH) and somatomedin-C (Sm-C) responsiveness to GRF (growth hormone releasing factor) and ACTH and cortisol responsiveness to CRF (corticotropin releasing factor) are unaltered with age, whereas CRF mediated DHEA secretion is greatly reduced, suggesting independent regulation of cortisol and DHEA secretion. Basal and TRH stimulated Prl secretion are increased in older vs. younger men. We have recently measured testosterone, testosterone binding, and gonadotropins in a large group of men of various ages with and without chronic illness and have shown that there is modest, but significant, decrease in both total and free plasma testosterone (T) with age, accompanied by increased FSH, but not LH. The effects of illness were a profound (compared with effects of aging) lowering of free (but not total) T in patients with benign disease, and lowering of both free and total T in patients with cancer. Continuing studies address the interrelationships among circulating estrogens and androgens, incidence of cardiovascular disease, and known cardiovascular risk factors, such as lipoprotein profile, obesity, and body fat distribution. We plan studies of the temporal regulation and feedback sensitivity of the ACTH-adrenal axis in the coming year.

IRP-LCP-298

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00023-10 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging. Pituitary, and Hypothalamic Function in Experimental Animals.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, Clinical Physiology Branch, NIA
(Unit II)COOPERATING UNITS (if any) Molecular Physiology and Genetics Section, Laboratory of
Cellular and and Molecular Biology, GRC
Department of Medicine, Francis Scott Key Medical Center
Departments of Medicine and Surgery, Johns Hopkins University School of Medicine

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Isolated cells from rat anterior pituitary glands are studied in vitro to compare their physiology in old vs. mature male and female rats. Production of TSH, prolactin, and gonadotropins (LH and FSH) are studied after treatment with specific stimulatory and inhibitory compounds, including TRH, LHRH, estrogen, dopamine, and iontophores. Deranged and altered function of aged rat pituitary cells in vitro has been found. Pretreatment of old and young rats for up to 24 hours with pulsatile doses of LHRH does not restore function of cells derived from old rats to levels observed for younger animals. Similarly, enhanced transmembrane transport of calcium ion with iontophore A23187 does not reverse the age-related defect in LH secretion. Data support our prior results suggesting an intrinsic age-related derangement in pituitary gonadotropic function. We have also described enhanced basal and estrogen stimulated Prl secretion by pituitary cells from old female rats, an increase in function disproportionate to the smaller increase in lactotrope number in aging rat pituitary glands. We have begun an investigation of the role of oxygen free radicals in the phenomenon of "in vitro" aging of Leydig (testosterone-secreting) cells. Preliminary experiments have demonstrated isolated Leydig cells to have lower activity of the protective enzyme, copper-zinc superoxide dismutase, than cells derived from seminiferous tubules, which normally surround (and may protect) Leydig cells from superoxide damage in vivo.

IRP-LCP-304

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00202-3 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physical Activity, Body Weight, Age, and Coronary Risk Factors

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Andrzej Ziemba, Ph.D.	Visiting Fellow, LCP, NIA
Jerome L. Fleg, M.D.	Staff Cardiologist, LCS, NIA
Reubin Andres, M.D.	Chief, Metabolism Section, LCP, NIA
Patricia Coon, M.D.	Medical Staff Fellow, LCP, NIA
Denis Muller	Metabolism Section, LCP, NIA
Jordan Tobin, M.D.	Chief, Applied Physiology Section, LCP, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.80

PROFESSIONAL:

0.50

OTHER:

0.30

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Risk factors for coronary artery disease (CAD) include age, metabolic and cardiovascular factors (hyperlipidemia, hyperglycemia, hypertension) and also certain living habits (diet, cigarette smoking, and physical activity level). Overweight is known to be associated with these factors. More recently, the pattern of fat distribution is emerging as an important contributory variable. Data obtained on participants in the Baltimore Longitudinal Study of Aging (BLSA) have been analyzed. The Body Mass Index or BMI (weight/height²) was used as an index of overweight and the waist:hip circumferential ratio (WHR) as a measure of fat distribution pattern. Both bivariate and multiple regression techniques were used to assess interrelationships among the variables designated as "independent" (age, BMI, WHR, and physical activity level) as well as to assess their influence on the variables designated as "dependent" (serum lipid moieties, glucose tolerance, fasting plasma glucose and systolic and diastolic blood pressure). Habitual physical activity level was obtained from detailed activity history questionnaires completed on each visit since 1965 by most participants in the BLSA and maximal aerobic capacity, VO₂ max, has been assessed in the past two years. Neither the habitual activity level nor the VO₂ max had much independent effect on coronary risk factors except for the serum cholesterol level in men and systolic blood pressure response to exercise in women. Thus, although intensive physical activity can be shown under experimental laboratory conditions to alter many coronary risk factors in a favorable direction, in this study of a free-living population the effect of activity is minimal. These surprisingly negative results might be explained if physical activity exerts its effects in this population by acting on body weight, so that it loses its independent significance on multivariate analysis.

IRP-LCP-310

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 00204-3 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic Studies in the Baltimore Longitudinal Study of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres, M.D.	Chief, Metabolism Section, LCP, NIA
Jordan Tobin, M.D.	Chief, Human Performance Section, LCP, NIA
Judith Hallfrisch, Ph.D.	Senior Staff Fellow, LCP, NIA
Janette Busby, M.D.	Medical Staff Fellow, LCP, NIA
Patricia Coon, M.D.	Medical Staff Fellow, LCP, NIA
Donald Drinkwater, Ph.D.	Visiting Associate, LCP, NIA
Denis Muller, B.S.	Chemist, LCP, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

3.56

PROFESSIONAL:

1.66

OTHER:

1.90

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Aging is characterized by a host of changes in metabolic variables which have profound effects on disease development and on survival. The BLSA provides the opportunity to conduct analyses on these variables to relate them to other characteristics of the individual, and to analyze for long-term effects of these complex interactions. Variables which are potentially alterable by changes in life style characteristics (diet, body weight, activity level) are of especial importance in this respect. Normative data, possibly specific for age, are required and can only be determined rationally by analyses such as these. In the past year, dietary diary information has been obtained on 330 men and women. This will provide an update for the previous 1961-1975 dietary information. Glucose tolerance data on women were analyzed; the glucose dose is essentially that recommended by WHO but with an adjustment for body size (40g/2 surface area). There were several interesting results: (1) the phase of the menstrual cycle does not influence glucose tolerance; (2) there is a progressive deterioration of tolerance with age from the 20's through the 70's; (3) women on oral contraceptive agents had poorer tolerance while women on estrogen replacement had better tolerance than their age peers. Erythrocyte and hemoglobin levels show no age changes in women, but men show a progressive increase in red cell size and decrease in erythrocyte hemoglobin concentration with aging.

IRP-LCP-313

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00205-3 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Recommended Weight Tables: A Synthesis of the Literature

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres, M.D.

Chief, Metabolism Section, LCP, NIA

Jordan Tobin, M.D.

Chief, Human Performance Section, LCP, NIA

Larry Brant, Ph.D.

Statistician, Human Performance Section, LCP, NIA

Denis Muller, B.S.

Chemist, Metabolism Section, LCP, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

0.35

0.15

0.20

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☒ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The issue of the effect of age on the recommended range of weights-for-height remains controversial. The major controversy involves the question of adjustment of recommended weights for age. The widely used Metropolitan Tables, most recently revised in 1983, are said to be applicable to ages 25 to 59 years. A re-analysis of data from the insurance industry (published in Build Study 1979) and a comprehensive collation of all pertinent studies from the world's literature has been previously accomplished. These analyses showed the necessity of modifying recommended weight-for-height for specific age groups, at least up to the 60-69 year decade. There has developed sufficient concern over the inadequacies of the Metropolitan 1983 tables that the Life Sciences Information Office of the Federation of American Societies for Experimental Biology held a planning meeting in July 1986 to discuss their possible role in providing new weight tables which would in essence have the imprimatur of FASEB. Dr. Henry Sebrell, former Director of the National Institutes of Health, was a moving force in the development of this role for FASEB. Our role in this effort is as Consultant to FASEB and, ultimately, providing them with the analyses which we have previously conducted using weighted quadratic correlational analyses for a number of the most important published studies in this field.

IRP-LCP-317

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00206-2 LCP
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Aerobic Exercise and Age: Metabolic, Hormonal, and Cardiovascular Responses		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
Andrzej Ziemba, Ph.D. Visiting Fellow, LCP, NIA Jerome Fleg, M.D. Scientist, LCP, NIA Reubin Andres, M.D. Chief, LCP, NIA Edward G. Lakatta, M.D. Chief, LCP, NIA S. Mitchell Harman, M.D. Scientist, LCP, NIA		
COOPERATING UNITS (if any) Ellen Rogus, Ph.D. Francis Scott Key Medical Center, JHH		
LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology		
SECTION Metabolism Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS 1.20	PROFESSIONAL 0.70	OTHER 0.50
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Physical working capacity decreases progressively during adult life. Contributing to this decline are decreases in function of the cardiovascular and pulmonary systems as well as a decrease in muscle mass. It is our hypothesis that decreased ability to perform physical work in the elderly is also associated with changes in the hormonal regulation of blood "fuel" regulation during exercise. The purpose of the present study is to examine the effect of age on plasma levels of glucose, free fatty acids (FFA) and of hormones responsible for regulating energy stores (catecholamines, glucagon, insulin) both at rest and during prolonged exercise. Plasma levels of glycerol, triglycerides and lactic acid are also measured. Exercise is accomplished by progressively increasing levels of treadmill walking. Subjects walk for 10 minutes at each of 3 exercise levels, 40, 50 and 60% of their previously determined maximal oxygen consumption (VO_{2max}), and for 30 minutes at 70% of VO_{2max} . Thus, duration of an exercise session is 1 hour. Blood samples for metabolite and hormone determinations are taken before exercise, at the end of each exercise stage, and 15 minutes after its termination. Samples of expired air are obtained before exercise, during the final 2 minutes of each submaximal workload and at the end of the recovery period for measurements of minute ventilation, oxygen consumption, carbon dioxide production, and respiratory quotient. The ECG is monitored continuously during the entire experimental period. Healthy subjects are selected from participants in the Baltimore Longitudinal Study of Aging according to the following criteria: no evidence of cardiovascular or other significant disease, negative treadmill maximal exercise test, no cardioactive medication, no cigarette smoking, non-obese and normotensive. Twenty-four men covering the adult age span have completed the protocol. Results will be analyzed in the coming year. Preliminary results on serum testosterone levels (basal and at the end of exercise) in the first 19 men show that both original levels and responses are highly positively correlated with the level of physical fitness (VO_{2max}) of the participants.		

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00207-2 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isometric Exercise and Age: Cardiovascular-Sympathoadrenal-Metabolic Responses

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Andrzej Ziemba, Ph.D.

Visiting Fellow, LCP, NIA

Reubin Andres, M.D.

Chief, Metabolism Section, LCP, NIA

Patricia Coon, M.D.

Medical Staff Fellow, LCP, NIA

COOPERATING UNITS (if any)

Andrew Goldberg, M.D.

Francis Scott Key Medical Center, JHH

Ellen Rogus, Ph.D.

Francis Scott Key Medical Center, JHH

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.60

PROFESSIONAL:

0.30

OTHER:

0.30

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Static (isometric) muscle contractions are common components of effort in performing daily activities. The problem of static exercise becomes important since isometric contractions cause marked increases in blood pressure and catecholamine levels. This study is designed to describe the relationships among age, sex, race, body weight, pattern of body fat distribution, level of physical fitness, and static exercise responses. The subjects for the study are selected from four volunteer groups: participants in the Johns Hopkins Academic Teaching Nursing Home, the Baltimore Longitudinal Study of Aging (BLSA), the Senior Athletes Study and volunteers working in this environment. They are divided into four age groups: 20-45, 45-59, 60-74 and 75 and over years. They range in obesity from lean to moderately obese and are further subdivided into subgroups of subjects representing upper and lower body segment type of obesity. The experimental protocol is the same for all subjects: sustained hand-grip exercise on a hand dynamometer at 30% of their individual maximal voluntary force to fatigue (usually 3 - 6 minutes). Before the test, at one minute intervals during the test, and 3 minutes after its termination, blood pressure, heart rate and blood samples for catecholamines, glucose and free fatty acids are taken. To date, a total of 170 subjects have been studied from several population groups. The goal of recruiting 160 subjects has just been surpassed and analyses of the results will be conducted in the coming year.

IRP-LCP-323

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00208-2 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging, Obesity, Sedentariness and Endocrine-Metabolic Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Donald Drinkwater, Ph.D. Visiting Fellow, LCP, NIA
Andrzej Ziemba, Ph.D. Visiting Fellow, LCP, NIA
Reubin Andres, M.D. Chief, Metabolism Section, LCP, GRC, NIA
Patricia Coon, M.D. Medical Staff Fellow, LCP, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center, The Johns Hopkins Hospital
Andrew Goldberg, M.D. Eugene Bleecker, M.D. Loretta Lakatta, R.N.
Ellen Rogus, M.D. Adriane Kozlovsky, R.D.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.70

PROFESSIONAL:

0.80

OTHER:

0.90

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Obesity, sedentariness and aging are known to be associated with hyperlipidemia, glucose intolerance, and altered sympathoadrenal responsiveness. In order to examine the interrelationship of age, adiposity, and physical fitness to endocrine-metabolic function, a study was designed to examine glucose and lipid metabolism and sympathoadrenal function in obese sedentary men aged 45-85 years at entry into the study and again after either weight reduction or aerobic training. The three areas of endocrine-metabolic function being studied are: 1) glucose tolerance and insulin sensitivity studied by the euglycemic clamp technique; 2) lipoprotein metabolism as assessed by measuring lipoprotein lipid profiles, HDL subspecies levels and lipoprotein lipase activity in postheparin plasma and adipose tissue; and 3) sympathoadrenal responses to isometric exercise (handgrip), upright posture, oral glucose challenge, and hyperinsulinemia during a euglycemic clamp. At this time, 48 participants have completed the baseline metabolic studies and have been randomized to either the weight reduction or aerobic exercise training intervention groups. The baseline studies indicate that these men have low levels of physical fitness, 25-30% have impaired glucose tolerance, and many are insulin resistant and have low plasma levels of HDL cholesterol. Twelve subjects have completed the weight loss program and undergone repeat metabolic testing. With weight loss there was a significant improvement in a number of the metabolic parameters with no change in their maximal aerobic capacity. Two subjects are trained and are now being retested. There are currently 14 subjects in the weight loss group and 20 in the exercise training program. They should be ready for retesting during the next 6-8 months. An additional 20 subjects are in the initial phases of baseline testing.

IRP-LCP-326

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00209-2 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and Cardiovascular, Endocrine and Metabolic Function in Master Athletes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Donald Drinkwater, Ph.D. Visiting Fellow, LCP, NIA
 Patricia Coon, M.D. Medical Staff Fellow, LCP, NIA
 Janette Busby, M.D. Medical Staff Fellow, LCP, NIA
 Reubin Andres, M.D. Chief, Metabolism Section, LCP, NIA
 Edward Lakatta, M.D. Chief, Laboratory of Cardiovascular Sciences, NIA
 Jerome Fleg, M.D. Scientist, LCS, NIA

COOPERATING UNITS (if any)

Francis Scott Mey Medical Center, Johns Hopkins University
 Department of Medicine, Johns Hopkins University
 The Johns Hopkins School of Hygiene and Public Health

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

2.25

1.40

0.85

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Endurance exercise training elicits physiological adaptations which increase the functional capacity of various organs. Older, physically well-trained "master" athletes tend to have a cardiovascular functional capacity (maximal oxygen consumption, VO_{2max}) which more closely approximates that of much younger individuals than that of their sedentary peers. They also have higher levels of high density lipoprotein (HDL) cholesterol, lower percent body fat and their tissues are more insulin sensitive than that of age-matched sedentary controls. To examine the interrelationship of age and physical fitness to endocrine-metabolic function, a study was designed to examine serum lipid profiles, lipid metabolism, glucose metabolic rates and insulin sensitivity, and cardiovascular function in healthy lean older men (>60 yrs), who are free of detectable coronary artery disease or metabolic dysfunction, and who have a wide range (25-50+ ml/kg.min) of VO_{2max} . To evaluate the specific role of training on metabolic and cardiovascular function, highly trained individuals will be de-trained over a 3 mo period; sedentary and less active subjects will be trained over a 6-9 month period. Thus, both groups will achieve a common level of VO_{2max} . Endocrine-metabolic function studies include: 1) glucose tolerance, beta cell sensitivity, and insulin sensitivity using oral glucose challenge (OGTT) and euglycemic and hyperglycemic clamp techniques, 2) lipoprotein metabolism and lipoprotein lipase activity, and 3) sympathoadrenal responses to isometric exercise (handgrip), to cycle exercise, and to lower body negative pressure. To date baseline fasting glucose and lipid profiles have been obtained on 65 participants. Sixty-two subjects have had oral glucose tolerance tests, and 54 of the men qualified have undergone an initial treadmill screening test and maximal oxygen consumption (VO_{2max}) test, 41 have undergone a second VO_{2max} test and thallium scans, 6 have undergone hyperglycemic clamps with measurements of insulin receptor binding, 7 have undergone multigated cardiac blood pool scans and 8 have had HDL subfraction analysis with measurement of postheparin plasma lipoprotein lipase activity.

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00210-1 LCP

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Control of Cell Proliferation in Cachectic Elderly With & Without Decubitus Ulcers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Roy Verdery, M.D.

Medical Staff Fellow, LCP, NIA

COOPERATING UNITS (if any)

Andrew P. Goldberg, M.D., Associate Professor, Medicine and Geriatrics
Francis Scott Key Medical Center, Johns Hopkins University
Teaching Nursing Home Pilot Grant

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.27

PROFESSIONAL:

0.22

OTHER:

0.05

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is designed to test the hypothesis that patients with cachexia, characterized by low lean body mass, anemia, hypoalbuminemia and/or hypocholesterolemia have impaired cell growth and metabolism because of low levels of a cellular growth factor, elevated levels of an inhibitory factor or low circulating lipoprotein levels. In *in vitro* systems using fibroblast cell proliferation, measured by ^3H -thymidine incorporation into DNA, is being used to assay plasma and sera from elderly subjects for growth stimulatory or inhibitory levels. This project may give significant insight into the mechanisms causing weight loss and promoting the occurrence of decubitus skin ulcers in the elderly.

IRP-LCP-338

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00700-01 LMG

PERIOD COVERED

March 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Genetic linkage analysis of age-related disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: E.L. Schneider

Acting Branch Chief

LMG, NIA

Others: J. White

Research Associate

LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA, (C.C. Plato)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

0 as yet

CHECK APPROPRIATE BOX(ES)



(a) Human subjects



(b) Human tissues



(c) Neither

☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The recent discovery by Alec Jeffreys of minisatellite DNA sequences that are highly polymorphic has made it possible to genetically "fingerprint" individuals by Southern hybridization of their DNA. Even very closely related people will show some differences in the size of the approximately 50 distinctive bands seen in a typical pattern. By definition, each of these bands is in close genetic linkage to some portion of the chromosome and therefore to genes that might be involved in disease. Our plan in this project is to "fingerprint" a large number of BLSA participants using this technique, and to try to identify specific bands that may be linked to specific patterns of age-related physiologic changes and/or age-related disease.

IRP-LMG-345

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00701-01 LMG

PERIOD COVERED

February 1, 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of DNA repair and aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: E.L. Schneider

Acting Chief

LMG, NIA

Others: N.P. Singh

Visiting Scientist

LMG, NIA

Peter Cerutti

Consultant

LMG, NIA

COOPERATING UNITS (if any)

Peter Hanawalt, Stanford University

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

National Institute on Aging, NIH, Baltimore, MD 21224

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:

0.1

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The focus of this study is to examine if alterations exist in the abilities of human cells to repair DNA damage. The emphasis of these studies will be to examine isolated cell populations that are functionally important to aging.

IRP-LMG-347

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00702-01 LMG

PERIOD COVERED

May 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of in vivo aging on neoplastic transformation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: E.L. Schneider

Acting Chief

LMG, NIA

Others: T. Kunisada

Fogarty Fellow

LMG, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

0 as yet

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The relationship between aging and carcinogenesis is being explored by transforming cells derived from young and old animals with various oncogenes. The rates of immortalization and transformation will be examined to determine if older cells respond differently from younger cells. Cells from several species will be examined, cells from different tissues in the same animal will be compared, and different combinations of oncogenes will be used.

IRP-LMG-349

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00703-01 IMG

PERIOD COVERED

January 1, 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Basis for Decreased Immune Function in Aging
Humans and Rats

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: Nikki J. Holbrook Senior Staff Fellow LMG, NIA
 Edward L. Schneider Acting Chief LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, Clinical Immunology
Section, NIA, (Dr. William Adler)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.3

PROFESSIONAL:

.4

OTHER:

0.9

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It is well established from both animal and human studies that there is a general decrease in immune function that occurs with aging. This project focuses on examining the cause(s) for this decline at the molecular level. Of particular significance is the decline in production of Interleukin 2 (IL-2), a lymphokine absolutely required for the proliferation of certain T cell populations. A primary objective of these studies is to determine whether the decline in IL-2 protein is accompanied by decreased expression of IL-2 mRNA. If so (and preliminary evidence indicates that this is the case), then we will attempt to determine what factors are responsible for the decreased IL-2 mRNA synthesis and whether or not they can be reversed. In addition, these studies will include examination of the expression of two additional genes with aging, both of whose regulation is intimately linked to IL-2. These are the IL-2 receptor and gamma interferon, another lymphokine whose expression is induced by IL-2.

IRP-LMG-351

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00704-01 IMG

PERIOD COVERED

June 22, 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Genetic Analysis of Alzheimer's Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	J. Milecki	Visiting Scientist	LMG, NIA
	E.L. Schneider	Acting Chief	LMG, NIA

COOPERATING UNITS (if any)

Dementia Research Service, Division of Chronic and Degenerative Diseases, Cornell Medical College (J. Blass, R. Shue)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

0 as yet

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Dr. John Blass at Cornell has shown that the activity of three thiamine-dependent enzymes--transketolase, alphaketoglutarate dehydrogenase, and pyruvate dehydrogenase--are decreased in two dementias, Wernicke-Korsakoff Syndrome and Alzheimer's disease. In general, this decrease occurs in body tissues not directly affected by the disease process; this suggests that inactivation of these enzymes is not simply an effect of the underlying pathology but may be intimately related to the cause of each disease, perhaps directly or perhaps as a predisposing factor.

The goal of this project is to clone the genes for these enzymes by screening cDNA expression libraries from human brain and liver with antibodies made by the Blass group and with synthetic oligonucleotides whose sequence will be derived from microsequencing of purified protein provided by the Blass group. The cloned DNAs for these genes will then be used as probes to analyze the structure and function of the genes in Alzheimer and Wernicke patients versus normal controls.

IRP-LMG-354

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00705-01 LMG

PERIOD COVERED

To begin September 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of a gene involved in shutting off cell growth.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	Mark Nuell	Staff Fellow	LMG, NIA
	E.L. Schneider	Acting Chief	LMG, NIA

COOPERATING UNITS (if any)

Dept. of Virology, Baylor College of Medicine (J.R. Smith)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

0 as yet

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Smith at Baylor has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into the same cell type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We plan to clone this mRNA by hybrid selection screening of a cDNA library; and then to analyze the structure and expression of the gene.

IRP-LMG-358

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00706-01 IMG

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Transcriptional Control Elements in the Gibbon Ape Leukemia
Virus LTR

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: Nikki J. Holbrook Senior Staff Fellow LMG, NIA

Others: Alberto Gulino Visiting Fellow LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Pathology, NCI (Drs. David Levens and John Quinn);
Laboratory of Molecular Immunoregulation, NCI (Dr. Francis
Ruscetti)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

1.0

.8

.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The goals of these studies are: (1) to identify and localize the transcriptional regulatory sequences within the long terminal repeats (LTRs) of different gibbon ape leukemia virus (GALV) strains; (2) to compare the relative transcriptional ability of the different strains and examine their tissue specificity of expression; and (3) having identified the regulatory sequences, to isolate and purify the trans-acting cellular factors which interact with these sequences to enhance the transcriptional activity.

IRP-LMG-360

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00707-01 LMG*

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Interleukin 2 Gene Expression in Lymphoid and
Nonlymphoid Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: Nikki Holbrook Senior Staff Fellow LMG, NIA

Others: Alberto Gulino Visiting Fellow LMG, NIA

COOPERATING UNITS (if any)

E.I. duPont Glenolden Laboratory, Dr. Yuan DeVries

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.3

PROFESSIONAL:

.9

OTHER:

.4

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

This project is focused at understanding the basic control mechanisms responsible for expression of the human interleukin 2 (IL-2) gene. Particular items within this study include (1) expression of the human IL-2 gene in mouse fibroblasts with DNA-mediated transfer; (2) mechanism for the activation of IL-2 expression in MLA 144 cells by a retrovirus insertion in the gene; and (3) role of 3' sequences in controlling IL-2 expression.

*formerly listed under NCI - 201-CB-00

IRP-LMG-363

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00708-01 LMG

PERIOD COVERED

July 1, 1986 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Identification of age-related transcripts in the mouse

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: D.B. Danner

Senior Staff Fellow

LMG, NIH

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

0 as yet

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Many changes in the levels of various enzymes have been found as a function of age. Typically, these changes are small, on the order of three-fold or less. It would be of value to have genes that change much more dramatically with age--perhaps several orders of magnitude--as markers for the aging process. It would be especially useful to have different markers of this type for different tissues; this would allow us to follow segmental aging changes. Finally, if such genes are directly controlled by some cellular program for aging, their isolation may allow us to get a closer look at this program.

Our approach to this analysis is to make cDNA libraries from young (3 month) and old (26 month) mice from the GRC colony. These libraries will be compared by hybridization techniques to see what RNA messages are present in high copy in one library but not in another. The structure and tissue-specific expression of these messages will then be examined.

IRP-LMG-367

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00709-01 IMG

PERIOD COVERED

To begin September 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of changes in hormone expression with age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	David Stewart	Research Associate	LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA (S.M. Harman, M. Blackman); Laboratory of Cellular and Molecular Biology, NIA (G. Roth).

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

0 as yet

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- | | | |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors | | |
| <input type="checkbox"/> (a2) Interviews | | |

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Harman and Blackman here at the NIA have shown that stimulated levels of luteinizing hormone decline with age in the rat pituitary, and Roth, also here, has shown that stimulated levels of prolactin increase in the same system. We will be asking the question whether these age-related hormone changes are reflected in the level of messenger RNA produced by the hormone genes. This will be done by quantitative hybridization analysis of pituitary messenger RNA using cloned hormone gene probes. If message levels are altered, we will proceed to ask whether the changes are at the level of the gene or in the regulatory pathway controlling the gene. This will be done by assaying the expression of a control exogenous hormone gene in the environment of the old and young cell. This analysis should ultimately allow us to pinpoint the defect that aging produces in this regulatory circuit, and may have important implications for the effect of aging on other regulated genes.

IRP-LMG-370

National Institute on Aging
Report of Chief, Laboratory of Neurosciences
Program Overview
1985-1986

The Laboratory of Neurosciences (LN) at the National Institute on Aging was formed in 1978, and has embarked on a program of research on the central and peripheral nervous systems in health, aging and disease, including dementia. In 1982, the Laboratory was divided into two sections -- a Clinical Section on Brain Aging and Dementia, and a Basic Section on Cerebral Physiology and Metabolism. The Clinical Section is located at the Clinical Center in Bethesda and is directed by Dr. Robert Friedland. Furthermore, in September 1982, a six bed patient care unit was established for an inpatient program to study patients with Alzheimer's and other dementias as well as normal subjects. The unit has temporary use of the 12E ward in the Clinical Center (Bethesda), and hopefully in the near future will be given a permanent ward appropriate for the program. This issue remains unresolved, however. An Outpatient Dementia Clinic was also started in 1982, as a means to screen subjects for the inpatient protocols and to establish methods for the differential diagnosis and staging of the various dementias. The Basic Section of the Laboratory moved to Bethesda in March 1984, and provides, together with the Clinical Section, a concerted program in the neurosciences.

This report summarizes the following projects: (A) Brain function in aging and dementia, (B) Functional interactions between brain regions, (C) Neuropsychology in aging and dementia, (D) Neurological function in aging and dementia, (E) Genetics and natural history of Alzheimer's disease, (F) Brain anatomy in aging and dementia, (G) Cerebrospinal fluid chemistry in aging and dementia, and (H) Clinical pharmacokinetics and pharmacodynamics. These projects were conducted primarily by members of the Clinical Section on Brain Aging and Dementia.

Projects conducted mainly by the Basic Section on Cerebral Physiology and Metabolism include: (I) Cerebral metabolism, relation to brain function and aging, (J) Brain lipid metabolism, relation to function and aging, (K) Regulation of gene expression in brain aging and dementia, (L) Brain markers of aging and dementia, (M) Blood-brain barrier and central nervous system function, (N) Transport systems at the blood-brain barrier, (O) Analytical methods and pharmacokinetics, (P) Pharmacology of central and peripheral catecholaminergic systems, (Q) Neuronal development in culture, (R) Peripheral nerve and blood-nerve barrier, and (S) Mechanisms of blood vessel regression.

A. Brain Function in Aging and Dementia.

In order to examine brain function during healthy aging and in disease states, the major thrust of the clinical program has been to measure cerebral metabolism by means of a new procedure recently introduced to the Clinical Center, positron emission tomography (PET). In the last five years, the LN has established and validated the PET procedure so as to obtain accurate and consistent measures of regional cerebral metabolic rates for glucose ($rCMR_{glc}$) under standardized and reproducible experimental conditions in humans.

1. Healthy aging. 18F-2-deoxy-D-glucose (FDG) was injected intravenously in 49 healthy men between the ages of 21 and 83 years, as a positron-emitting analogue of glucose, to examine regional cerebral metabolic rates for glucose (rCMRglc). PET scanning was performed under resting conditions, when the subjects' eyes were closed and ears plugged with cotton. rCMRglc was not correlated significantly with age in 31 pairs of bilaterally symmetrical and in 3 midline brain regions ($p > 0.05$), and mean hemispheric glucose utilization also was not correlated significantly with age in the 49 subjects. Quantitative analysis of computer assisted tomographic (CT) scans showed that brain atrophy in the elderly accounted for no more than 13% of the variance in global metabolism. When brain atrophy was taken into account, there also was no relation whatsoever between global cerebral metabolism and age. The age invariance of cerebral glucose utilization in healthy men indicates that, in the absence of disease, compensatory mechanisms exist in the senescent human brain to counteract effects of morphological and neurochemical age changes which have been reported. This work was done by N. Schlageter and B. Horwitz.

2. Alzheimer's disease. rCMRglc was examined with PET in patients with Alzheimer's disease (AD) of different severities, as measured by scores on the Folstein Minimental Examination and Wechsler Adult Intelligence and Memory Scales. Absolute values for rCMRglc in the frontal, parietal, temporal and occipital lobes did not differ from values in healthy controls in AD patients with mild or moderate dementia. The severely demented group showed metabolic deficits in the left frontal and bilateral parietal and temporal regions. However, ratios of rCMRglc to sensorimotor rCMRglc revealed significant decrements in the parietal lobes in the mild and moderately demented patients, whereas the severely demented patients had decrements in the temporal and frontal lobes as well. Our findings suggest that memory and cognitive deficits in mild-moderate AD patients are accompanied by reduced metabolism in association areas of the parietal lobes, relative to metabolism in primary sensory-motor areas, and that clear reductions in absolute metabolic rates occur only in severely demented patients.

We also studied rCMRglc in 17 patients with AD and in 17 healthy controls, using a method of analysis which separates subjects into groups on the basis of similar patterns of metabolism, rather than diagnosis (Q component analysis). Three groups were identified, two composed mainly of control subjects, and one of AD patients. The AD pattern consisted of an anterior to posterior gradient of decreasing metabolic activity, with relative sparing of anterior medial frontal, primary visual and subcortical regions. The pattern was not related to severity of dementia, and corresponds to findings of parietal lobe deficits in AD (see above). It remains to be seen whether the pattern is unique to patients with AD, in which case it may be of diagnostic use. This work was done by Dr. C. Grady.

Left-right asymmetry of cerebral metabolism (see Section C, below) in mildly and moderately demented AD patients was shown to be unchanged and correlated with appropriate neocortically-mediated neuropsychological deficits (syntax comprehension and visuospatial deficits) when redetermined over periods of up to two years. These results demonstrate that the metabolic asymmetries have a consistent basis in cerebral neuropathology, and may reflect asymmetrical numbers of neuritic (senile) plaques that are seen in brains of AD patients postmortem. This work was done by C. Grady and J. Haxby.

Repeated PET scans in a 57 year old patient with documented family history of Alzheimer's disease, during a period of two and one-half years, demonstrated that memory loss preceded a significant reduction in brain metabolism in any neocortical area. Later reductions in parietal lobe metabolism were accompanied by changes in language and visuospatial performance.

3. Adult Down syndrome. At least 150 developmental abnormalities and diseases may affect the human brain at an early age and cause mental retardation. Of these, Down syndrome (DS) is the most common with an established etiology. Brains of young adult DS subjects show no consistent morphological abnormalities, but brains of older DS subjects have pathological and neurochemical changes that also characterize Alzheimer's disease. M. B. Schapiro used PET to measure $rCMR_{glc}$ in 13 young adult DS subjects aged 19-33 years, and in four old DS subjects aged 47 to 63 years, who showed evidence of cognitive reductions. Hemispheric and many regional metabolic rates in young DS subjects were 20-30% higher than in age matched controls, whereas metabolic rates in the older DS subjects were less than in the younger DS subjects and did not differ from values in age-matched controls. This study demonstrated that DS is associated with an elevated brain oxidative metabolism, possibly reflecting excessive and inefficient use of glucose. Aging in DS is accompanied by a decline in metabolism, corresponding to the decline in cognitive function and to reported neuropathology.

B. Functional Interactions Between Brain Regions.

1. Patterns of brain metabolism in healthy men. A matrix method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose ($rCMR_{glc}$), as determined with PET, in 40 healthy men, under reduced visual and auditory stimulation. Brain regions in one cerebral hemisphere were metabolically correlated with homologous regions in the other, reflecting functional connections via the corpus callosum. Regions in the frontal and parietal lobes were closely coupled with each other, but not with regions in the temporal and occipital lobes, which formed an independent coupled unit. At rest in healthy men, the brain demonstrates left-right regional metabolic coupling and, within each hemisphere, two independent interacting units, the frontal-parietal and occipital-temporal areas. Matrix analysis provides another way in addition to absolute metabolic rates to examine brain functional activity. This work was directed by B. Horwitz and R. Duara.

2. Age changes in brain metabolic pattern. The matrix method was applied to two subgroups (15 each) of healthy men (ages 21-32 years and 64-83 years). The analysis demonstrated fewer significant metabolic correlations for the older group, with reduced numbers of correlations between parietal lobe regions, and between parietal and frontal lobe areas. Thus, although $rCMR_{glc}$ is not correlated with age in healthy men (Section A), the pattern of $rCMR_{glc}$ differs between young and elderly. The reduced number of correlations may correspond with reductions in visuospatial abilities in the healthy elderly, and in other aspects of fluid intelligence.

3. Brain metabolic pattern in Alzheimer's disease. The correlation approach was applied to a group of 21 mostly mildly-to-moderately demented subjects diagnosed as have dementia of the Alzheimer's type (DAT), and to 21 age-matched controls. The DAT group differed significantly from controls in showing a loss of correlations between frontal and parietal lobes, and a loss of

homologous left-right correlations (14 out of 28 were missing, compared with 6 out of 28 for the controls). These missing homologous correlations correspond to asymmetry in metabolism between the two hemispheres (Sections A and C), which in turn correlates with lateralized neuropsychological deficits. They demonstrate a disconnection between the right and left hemispheres in Alzheimer's disease. This work was performed by B. Horwitz.

4. Functional coupling in the rat brain. Functional interactions among different regions of the rat brain were characterized by the matrix method for analysis of rCMR_{glc}. A large number of positive couplings were found between left-right homologous regions and between neocortical areas. The similarity between these findings and those in humans (see above) further supports use of the matrix method to examine patterns of functional brain activity. This work was performed by T. Soncrant and B. Horwitz.

5. Corpus callosotomy and brain metabolic pattern. To test the hypothesis that interhemispheric pathways passing through the corpus callosum mediate left-right homologous interactions, correlation coefficients were examined among 97 brain regions and their contralateral homologues in rats that had undergone callosotomy and in sham-operated controls. For interhemispheric (left-right) pairwise correlations, 1604 (65%) were smaller, whereas only 875 (35%) were larger in the callosotomized rats. Most homologous cortical and subcortical correlations were reduced. These findings are consistent with the known role of the corpus callosum in interhemispheric functional integration, and support the validity of correlation analysis for characterizing functional brain interactions in a given "state". This work was performed by T. Soncrant and B. Horwitz.

C. Neuropsychology in Aging and Dementia.

1. Healthy aging. J. V. Haxby demonstrated, in 40 healthy men aged 21 to 83 years, that age differences in performance on tests of general intelligence (Wechsler Adult Intelligence Scale) and of visual memory (Benton Visual Retention Test) were significantly less than differences reported in normative studies with these tests, suggesting that increasing prevalence of illness in the elderly contributes to age-related differences in normative standards for neuropsychological tests. Performance was not correlated significantly with regional cerebral metabolic rates for glucose (rCMR_{glc}), as measured with PET (see Section A). This lack of correlation supports the hypothesis that physiological and psychological cerebral functions are coupled only when both are under the limiting influence of disease.

2. Alzheimer's disease. J. Haxby examined 27 patients with Alzheimer's disease (AD) with mild, moderate or severe dementia, as indicated by a standardized Mini-Mental State examination. The mild and moderate groups demonstrated marked impairment of recent memory and of learning ability. In individual patients, language and visuospatial impairments were often of markedly disproportionate relative severity, suggesting that, aside from memory impairment, neuropsychological deficits associated with AD are heterogeneous.

In patients with moderate AD, the relative disproportion of language and visuospatial impairments, as measured by subtests of the Wechsler Adult Intelligence Scale and experimental tests of drawing and syntax comprehension, was significantly correlated with asymmetry of rCMR_{glc}. In patients with mild AD, such a

correlation did not hold. However, all patients with mild and moderate AD demonstrated a larger range of right-left metabolic asymmetries. Individual values for rCMRglc were not significantly related to asymmetrical cognitive performance in healthy controls or in mildly demented AD patients, but were so related in moderately demented AD patients, consistent with known functional neuroanatomy. In mildly demented AD patients with memory defects, metabolic asymmetries as measured with PET appear to precede measurable discrepancies of cognitive functions subserved by the neocortex.

D. Neurological Function and Behavior in Aging and Dementia.

1. Audiology. Studies of central auditory functions using the staggered spondaic word (SSW) test, showed that AD patients performed worse on this dichotic hearing test than did age-matched controls. It also was demonstrated, using computer assisted tomography (CT) of the brain, that increased atrophy of both temporal lobes was associated with poorer SSW performance. A unilateral SSW ear deficit was associated with more atrophy in the contralateral hemisphere. These findings are consistent with evidence that this type of auditory processing is sensitive mainly to temporal lobe deficits in AD. This work was done in collaboration with A. Grimes of the Outpatient Department of the Clinical Center.

Further studies in AD patients demonstrated reduced performance, as compared with controls, on monotic degraded speech tests, as well as the dichotic SSW test. There was no relation between performance on the monotic tasks and cerebral atrophy or metabolism. These findings suggest that the dichotic nature of the SSW test is responsible for its relation to cerebral atrophy, and support our conclusion that AD patients have divided attention.

2. Motor activity and aging. J. W. Renfrew employed patient activity monitors (PAM) attached to the nondominant wrist, and self-report diaries, to examine hourly motor activity and sleep in 43 healthy men, aged 21 to 83 years, over 10 day periods, in their natural work and home environments. Counts/hour on the PAM were divided into high and low activity periods per day. The mean duration of low activity per day equalled 7.3 hr in the 40 subjects, as compared to 7.8 hr for sleep time as estimated from the diaries; neither parameter was correlated with age. Net counts per day, on the other hand, fell by 5% per decade, suggesting that motor activity but not sleep duration declines with age in healthy individuals. This work was performed in collaboration with T. R. Colburn (NIMH).

E. Genetics and Natural History of Alzheimer's Disease.

Outpatient dementia clinic. One hundred and fifty five patients who were admitted consecutively to our outpatient dementia clinic were given a diagnosis of primary degenerative dementia, multi-infarct dementia, mixed degenerative-vascular dementia, miscellaneous dementias or not demented. The multi-infarct dementia group differed from the primary dementia group on the Hachinsky Ischemic score, whereas other dementia tests did not distinguish among the dementia groups. Criteria and objective scores for making initial diagnoses of various dementias were established, prior to later neuropathological confirmation.

F. Brain Anatomy in Aging and Dementia.

1. Quantitative analysis of CT data. A computerized procedure was developed to quantify the volumes of cerebral cortical structures from data obtained with computerized transverse axial tomography (CT), in collaboration with the Division of Computer Research Technology. By means of an image processing procedure (DMORPH), the means and standard deviations of CT numbers of representative regions of cerebrospinal fluid, white matter and gray matter were determined for each CT scan. A CATSEG program used these means to define ranges for each tissue type, and to assign to each pixel in a scan one of the three categories. Volumetric estimates were obtained by summing over 7 consecutive scans in a 49 mm brain segment. Methods to evaluate surface areas of CT structures also were developed. This work was performed by J. DeLeo, H. Creasey, M. Schwartz.

2. Alzheimer's disease. In 22 male patients with AD (age range 45 to 84 yr), and 17 female patients (age range 55 to 81 yr), quantitative analysis of CT data demonstrated that the percentage of intracranial space occupied by gray matter was reduced, and that occupied by cerebrospinal fluid was increased, as compared to values in age matched healthy controls. With respect to the severity of dementia as measured by the Mini-Mental State Examination, the percentage of gray matter declined and the percentage of white matter increased. Mildly demented patients showed a significant increase in mean third ventricle volume compared to controls, whereas the moderately demented group showed as well less gray matter volume and a lower gray/white ratio. The severely demented patients showed, in addition, significant dilatation of the lateral ventricles. The findings demonstrate that brain atrophy can be quantitatively demonstrated with CT scans in AD patients, and that the extent of atrophy and ventricular dilatation is related to severity of dementia. This work was done by H. Creasey.

Twelve men and six women with dementia of the Alzheimer type (DAT) and twelve healthy male control subjects were studied over 6 months to 5 years with serial quantitative CT of the brain. In the male DAT patients, mean rates of enlargement of third ventricle volume and of total lateral ventricular volumes differed significantly from zero and from respective control rates. The female DAT patients also had significantly higher rates of enlargement of the third and total lateral ventricles. There was no overlap between the rates of lateral ventricular enlargement in DAT patients and controls. In men with DAT, the rate of neuropsychological decline correlated with the rate of enlargement of the third ventricle and of the right lateral ventricle. These results indicate that longitudinal quantitative CT studies can be used to distinguish DAT from control subjects. This work was done by J. Luxenberg.

3. Down syndrome. Adult Down syndrome (DS) subjects with trisomy 21 karyotype were examined by quantitative CT scanning, in relation to age matched healthy controls. In young DS subjects (21 to 35 yr), reductions were present in total intracranial volume and gray matter volume. However, when the volumes of gray matter and individual intracerebral structures were normalized to height, no significant differences were observed from controls. When young and old DS subjects were compared (older than 35 yr), an increased CSF volume was demonstrable, indicative of brain atrophy in the older patients. Thus, no gross differences exist between brains of young DS subjects and controls, after normalization for the established relation between brain size and height. Aging in DS, which is associated with reduced cognitive capacity and neuropathology, is

associated with evidence of brain atrophy. This work was conducted by M. Schapiro.

4. Adult autism. Nine adult males with autism were compared with age matched controls using quantitative CT. There were no statistically significant group differences on measures of cerebrospinal fluid, white matter, gray matter volumes, or subcortical nuclei volumes, indicating no gross anatomical abnormality in this syndrome. This work was done in collaboration with J. Rumsey (NIMH).

G. Cerebrospinal Fluid Chemistry in Aging and Dementia.

1. Markers of catecholamine metabolism. Concentrations of homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), norepinephrine (NE), and MHPG were examined in cerebrospinal fluid and plasma from 30 patients with AD and from 15 age-matched healthy controls. No statistically significant differences were found between the patients and controls in any of these metabolite concentrations. In addition, no consistent relation was demonstrated between metabolite concentrations and the severity of dementia, or between age and metabolite concentrations. Thus, lumbar cerebrospinal fluid concentrations of these markers of brain catecholamine metabolism are not good indices of brain function in relation to age or to AD.

2. Choline in Down syndrome. M. Schapiro and A. D. Kay measured cerebrospinal fluid concentrations of choline in young adults with Down syndrome (DS), and in age-matched healthy controls. The young DS subjects had significantly higher choline values, which could not be accounted for by differences in plasma choline levels. Increased spinal fluid choline suggests increases in the activity of the central cholinergic system in DS, and is not inconsistent with a report, from this laboratory that the cerebral metabolic rate for glucose is elevated in DS. This work was done in collaboration with I. Hanin.

3. Corticotropin releasing factor (CRF) in Alzheimer's disease. CRF is a 41-amino acid peptide which is present in brain regions, including the hypothalamus, amygdala and substantia innominata, regions which are reported to be affected in AD. Cerebrospinal fluid samples from 23 AD patients and 11 healthy age matched controls were assayed for CRF. In 11 of the 23 patients, and in 1 of the controls, CRF was below 12.5 pg/ml. CRF levels were significantly reduced in the cerebrospinal fluid of AD patients, indicating that this disease may be associated with selective loss of CRF-containing neurons. This work was directed by C. May.

4. Peptidyl-a-amidation activity in Alzheimer's disease. The peptidyl-a-amidation enzyme (PAM) is thought to be coreleased from neuronal secretory granules with amidated peptides, including CRF. PAM activity was significantly reduced in the cerebrospinal fluid of AD patients as compared to the cerebrospinal fluid of controls, consistent with the reported reduction in CRF, and suggesting that there is a selective loss or dysfunction in AD of brain neurons which produce amidated neuropeptides. This work was directed by C. May.

5. Blood-brain barrier in Alzheimer's disease. Disruption of the blood-brain barrier and immunologically-mediated injury to the brain have been proposed as pathogenic mechanisms in AD. These hypotheses were investigated by measuring concurrent cerebrospinal fluid and serum concentrations of albumin and

of immunoglobulin G (IgG) in 31 AD patients and in 20 controls. There were no significant differences in the CSF/serum ratios of albumin and of IgG between AD patients and controls, nor between the ratios of the ratios (IgG) index. Therefore, there was no evidence of blood-brain barrier breakdown or of abnormal central nervous system production of immunoglobulins in the AD patients.

6. Cerebrospinal fluid bipterin in Alzheimer's disease. Tetrahydrobiopterin, a cofactor in the hydroxylation of phenylalanine, tyrosine and tryptophan leading to the eventual synthesis of the monoaminergic neurotransmitters, dopamine, norepinephrine and serotonin, respectively, was significantly reduced in the cerebrospinal fluid of patients with AD, suggesting that a central bipterin and monoamine deficiency exists in this disorder. This work was performed by A. Kay and S. Kaufman.

7. Cerebrospinal fluid neuron specific enolase in Alzheimer's disease (AD). Neuron-specific enolase, a glycolytic enzyme enolase found in brain, was reduced in the cerebrospinal fluid of patients with AD. The results probably reflect loss of neurons in the course of AD.

H. Clinical Pharmacokinetics and Pharmacodynamics.

Serotonergic therapy in Alzheimer's disease. Zimelidine, a serotonergic reuptake blocker, was evaluated in AD patients. The drug significantly reduced cerebrospinal fluid concentrations of serotonin, but did not influence the concentration of 3-methoxy-4-hydroxy-phenylglycol, a major metabolite of norepinephrine. It had no effect on memory function, suggesting that a serotonergic mechanism does not contribute to memory defects in AD.

I. Cerebral Metabolism, Relation to Brain Function and Aging.

1. Regional cerebral blood flow in Beagle dogs of different ages. Regional cerebral blood flow (rCBF), a measure of brain functional activity, was determined in Beagles by the i.v. infusion of ^{14}C -iodoantipyrine, in relation to age. Reductions between 1 and 12 years of age were statistically significant only in 9 of 35 brain regions, and ranged from 11 to 25%. A majority of brain regions showed reductions in rCBF, by an average of 29%, in 14-15 yr old dogs, which also had cardiovascular and sensory-motor problems. The results demonstrate that cerebral functional activity is generally maintained during most of the adult life of the dog, but falls in extreme senescence in relation to disease. These studies correspond to our findings in humans with PET (see above). This work was conducted by H. Tabata.

2. Effects of cholinergic agonist on cerebral metabolism in rat. We measured rCMRglc with the 2-deoxyglucose (2DG) technique in 3 month Fischer-344 rats in response to various doses of the cholinergic agonist, arecoline. Animals were pretreated with methylatropine to prevent parasymphathomemetic side effects. rCMRglc increased in a dose-dependent manner in most brain regions, including those which mediated the tremor which also was produced. At low doses, rCMRglc was stimulated in the hippocampus and layers IV and VB of the cerebral cortex, which have high concentrations of muscarinic receptors. The results demonstrate where and to what extent brain metabolism is stimulated with a clinically-used cholinergic agonist. This work was conducted by G. Pizzolato and T. Soncrant.

3. Cholinergic function in relation to age. Male Fischer-344 rats, aged 3 or 24 months, were administered arecoline and rCMRglc was measured as noted above. Cerebral metabolic responses did not differ significantly between the two age groups, indicating that muscarinic post-synaptic receptor responses are intact in the senescent rat brain. This work was conducted by G. Pizzolato and T. Soncrant.

4. Metabolic responses of rat brain to a dopaminergic antagonist. Haloperidol, a neuroleptic dopaminergic antagonist, was given to 3 month old male Fischer-344 rats of different ages, at a high and low dose, following which rCMRglc was measured at different times. The time course of the rCMRglc response differed in relation to dose, and showed delayed decreases in rCMRglc between 30 and 90 min after haloperidol. The onset of the responses correlated with the time course of catalepsy, and corresponded to known pharmacokinetics of the drug. The results identify where and when haloperidol, a clinically used drug, acts within the brain. This work was conducted by G. Pizzolato and T. Soncrant.

5. Development of tolerance to the cerebral metabolic effects of haloperidol. Chronic exposure to neuroleptic drugs alters behavioral and functional brain parameters, and has been associated with the development of supersensitivity to dopaminergic agonists. Fischer-344 rats that received daily injections of haloperidol for 3 weeks showed reduced values for rCMRglc in regions of the mesolimbic dopaminergic system, but no catalepsy as noted in acutely treated rats. The general metabolic response was less than after acute administration. These results show that a reduced rCMRglc response corresponds to the tolerance that develops after continuous haloperidol treatment.

6. Age-associated decline in effect of haloperidol on rCMRglc. The peak effects on cerebral metabolism to haloperidol were significantly less in 33 mo old Fischer 344 rats than in 3 mo and 12 mo animals (see above for results in young animals). Furthermore, catalepsy was less in response to haloperidol in old than in young rats. On the other hand, brain concentrations of haloperidol were higher in old than in young rats, due to a slower rate of elimination of the drug. The age differences in the cerebral response to haloperidol correlate with known age-dependent structural and biochemical deficits of central dopaminergic function in the brain of the senescent rat, and suggest an imbalance between dopaminergic and cholinergic activity (see above). This work was conducted by G. Pizzolato and T. Soncrant.

7. Effect of phenobarbital on brain metabolism in the rat. The anesthetic, phenobarbital, was administered to rats at different doses, and rCMRglc was measured after 1 hr by the 2 DG technique. Lower doses of phenobarbital, which affected performance on a rotating cylinder, reduced rCMRglc significantly in brain regions involved with motor performance but not in cerebral cortical regions. Higher doses affected cerebral metabolism generally. The results demonstrate regional specificity of the phenobarbital metabolic effect at low doses, and indicate specific actions of this drug in relation to its early effect on motor behavior.

8. Effects of nicotine on brain metabolism in rats. Nicotine, a cholinergic agonist, was administered to awake rats and rCMRglc was measured with the 2-DG technique. The rats were pretreated with hexamethonium bromide. Nicotine, 1 mg/kg, elevated rCMRglc by an average of 25%, primarily at sites of central

nicotinic receptors. Higher doses produced tremor and elevated rCMRglc generally throughout the brain. The regional responses to nicotine corresponded to the cerebral distribution of specific central nicotinic receptors.

9. Effects of methiothepin on brain metabolism. Methiothepin, a serotonergic antagonist, reduced rCMRglc in relation to dose administered to awake rats. The effects at low doses were interpreted in terms of serotonergic autoreceptor blockage, which increases serotonin release and thereby enhances indirectly postsynaptic inhibitory effects of serotonin. The changes were accompanied by a reduced spontaneous motor activity, demonstrating a link between regional energy metabolism and functional brain activity.

10. Brain glucose utilization and age in Fischer-344 rats. We and others previously reported that rCMRglc declines between 3 and 12 months of age in awake Fischer-344 rats, but that regional cerebral blood flow (rCBF) is age-invariant during maturity and senescence in this strain. The results could mean that coupling between brainblood flow and metabolism is altered with aging. Alternatively, the "lumped constant" which relates the metabolism of glucose to that of ^{14}C -2-deoxy-D-glucose, in the procedure to measure rCMRglc, could decline. We demonstrated in fact that the lumped constant falls sufficiently between 3 and 24 months of age to make rCMRglc age-invariant. Thus, coupling between brain-blood flow and metabolism is unchanged during aging in the rat. This work was directed by H. Takei.

11. Brain oxidative metabolism during development. rCMRglc was shown to increase continuously, without peaking, between 7 days of age and maturity at 3 months in awake Fischer-344 rats. The time courses of regional increases demonstrated earlier maturation in posterior, phylogenetically older brain regions than in new telencephalic regions. However, no peak increment was noted at the period of maximum brain growth (20 days), indicating that energy metabolism does not closely reflect brain synthetic activity during neonatal development. This work was done by E. McCann.

12. Semi-automated method for quantitative densitometry in autoradiographs. T. Soncrant developed a method which has the advantages of reducing time required for data collection with manual methods, of providing easy retrieval of data and of formatting data for statistical analysis in the measurement of rCMRglc by quantitative autoradiography.

J. Brain Lipid Metabolism, Relation to Function and Aging.

1. Method to measure brain palmitate incorporation. A quantitative method was developed by A. Kimes to examine the uptake of an intravascular fatty acid, palmitate, into individual brain regions of awake rats. ^{14}C -palmitate was injected intravenously, and plasma concentrations of cold and radiolabeled palmitate were measured to decapitation at 4 hours. The transfer constant for radiotracer, equal to brain radioactivity divided by the integrated plasma palmitate radioactivity, was multiplied by the cold plasma palmitate concentration to give the flux of palmitate into brain, J_{pal}. Brain radioactivity was determined by quantitative autoradiography, and remained unchanged between 4 and 24 hours, indicating that ^{14}C -palmitate was incorporated into stable brain structures. J_{pal} was found to be proportional, within individual brain regions, to rCMRglc as measured with the 2-DG technique (see above). Palmitate uptake in gray matter exceeded uptake in white matter. The palmitate method makes it

possible to relate turnover of brain lipid structures to brain oxidative metabolism and function.

2. Mathematical model for brain incorporation of plasma palmitate. A three compartment mathematical model was developed by P. Robinson to interpret and calculate, from experimental data, the rate of palmitate uptake by brain from plasma, Jpalm. The model can be used to determine transfer constants between brain and blood, and to interpret time-dependent changes in brain radioactivity following the i.v. injection of ^{14}C -palmitate.

3. Effect of aging of the rat of Jpalm. H. Tabata demonstrated that Jpalm is age invariant in rats, aged 3 to 34 months. As the rate of incorporation of palmitate into the adult brain represents the lower limit for turnover of brain lipids, the results demonstrate that brain structural integrity is maintained during aging of the rat.

4. Uptake of palmitate by the brain of the developing rat. Jpalm was measured in awake Fischer-344 rats between the ages of 15 and 3 months. Jpalm rose between 15 and 20 days of age in gray and white matter regions, declined 4-5 fold in gray matter and 7-10 fold in white matter by 38 days, and reached adult levels by 3 months of age. The white/gray ratio for Jpalm declined significantly between 20 days and adulthood. The time course of Jpalm corresponds to the time course of myelination during development of the rat brain, when there are parallel changes in the rates of palmitate incorporation into gray and white matter regions. Jpalm clearly is a measure of brain lipid turnover and synthesis. This work was performed by H. Tabata.

K. Regulation of Gene Expression in Brain.

1. Cell free protein synthesis system from rat brain. A cell-free system, capable of initiating protein synthesis, was derived from the rat brain and characterized by J. Cosgrove. Optimal conditions were identified, and both 40S and 80S initiation complexes could be labeled using ^{35}S -methionine.

2. Aging and brain protein synthesis. J. Cosgrove, using the cell free system, demonstrated age invariance of brain protein synthesis capacity, and no age difference in the aggregation state of polyribosome profiles obtained from brains of 3 mo and 34 mo old Fischer-344 rats. These results agree with other findings in this laboratory that brain oxidative metabolism and palmitate incorporation generally are age invariant in the Fischer-344 rat, and point to compensatory mechanisms that maintain cerebral functional activity during aging, in the absence of disease.

3. Analysis of gene expression of local protein end products. A silver stain procedure was developed to detect abundant and moderately abundant brain proteins in 11 brain regions of Fischer-344 rats. The levels of most proteins were shown to be age invariant, but some in individual regions increased with age. These results suggest that local protein changes do occur with aging, and that they should be explored, despite the age invariance of overall protein synthesis. This work was conducted by J. Cosgrove.

4. Oncogene-related sequences in the rat brain as a function of age. Northern analysis with molecular biological techniques was used to measure total brain poly(A⁺) RNA in Fischer-344 rats between 3 and 23 months of age. The

total poly(A⁺) RNA was translated in vitro, and the amount of c-src protein synthesized (expression of brain RNA) was analyzed quantitatively and shown not to be related with age, indicating that this level of expression is unchanged with healthy aging in the rat brain. This work was directed by M. Matocha.

L. Brain Markers in Aging and Dementia.

1. Rats made diabetic by administration of streptozotocin showed decreases in activity of tyrosine hydroxylase, a synthetic enzyme for catecholamines, and increased concentrations of norepinephrine in various brain regions, including the thalamus and hypothalamus. The research, conducted by M. Bitar, indicates that diabetes can alter brain monoamine metabolism, and behaviors subserved by monoamine neurotransmitters.

2. Procedures were established at the Laboratory of Neurosciences for conducting appropriate autopsies of inpatients and outpatients who have died, and for providing neuropathological diagnoses.

M. Blood-Brain Barrier (BBB) and Central Nervous System Function.

1. Reversible osmotic opening of the blood-brain barrier.

a. Method and clinical application. In 1972, we first demonstrated that the blood-brain barrier (BBB) could be reversibly opened in animals by infusing a hypertonic solution of a water soluble nonelectrolyte (e.g., urea, mannitol, arabinose) into the internal carotid artery. The effect later was shown to be caused by osmotic shrinkage of cerebrovascular endothelial cells, with consequent widening of interendothelial tight junctions. In later years, we experimentally refined the osmotic method, quantified changes of cerebrovascular permeability in relation to infusate concentration and infusion time, and demonstrated reversibility of the osmotic effect. We showed that, when the BBB is opened osmotically, brain metabolism is transiently stimulated, brain edema occurs and metabolism is uncoupled temporarily from cerebral blood flow. Thus, BBB integrity must be maintained continuously for normal cerebral function. In diseases which affect BBB integrity in man, changes in consciousness may be related to these central effects of BBB disruption.

On the basis of the animal studies, we initiated a Phase I clinical protocol with E. A. Neuwelt (Oregon Health Sciences Center) to apply the osmotic procedure in patients with metastatic brain tumors, so as to allow methotrexate or other antineoplastic drugs into the brain. We demonstrated with computer assisted tomography that the BBB can be opened reversibly in humans without producing apparent neurological damage. The clinical study is being continued to see whether the osmotic procedure will be efficacious for prolonging survival of patients with brain tumors.

b. Pore mechanism for BBB opening. To further support the tight junctional as compared to the transcellular channel or vesicular mechanism, Y. Z. Ziyilan and P. J. Robinson examined the time course of cerebrovascular permeability to nonelectrolytes of different size, ¹⁴C-sucrose (mol. wt. = 340 daltons), ³H-inulin (mol. wt. = 5200) and ³H-dextran (mol. wt. = 79000 or 200,000), following osmotic barrier opening. Whereas the barrier was opened to all of the radiotracers immediately following the intracarotid injection of 1.8 molal arabinose solution in rats, the rate of closure was faster the larger

the molecule. Size differentiation during recovery supports the tight junctional mechanism rather than the vesicular mechanism, as vesicles are much larger than any of the tracers and would not be selectively permeant to smaller as compared to larger molecules. Furthermore, the differential rate of barrier reclosure suggests that, if drugs are to be used with the osmotic procedure, they should be administered within a few minutes after hypertonic infusion.

c. Reversible modification of blood-brain barrier permeability in mice.

A number of disease models have been developed in mice in which it would be useful to study central nervous system effects of therapeutic agents normally excluded from the brain. Therefore, the osmotic method was extended to unilaterally and reversibly open the barrier in mice, using appropriate flow rates for carotid infusion and appropriate arabinose concentrations. The effect was shown to be reversible. This work was conducted by W. R. Fredericks.

d. Role of bilirubin in neonatal kernicterus.

We determined clearance of bilirubin from the rat brain following reversible osmotic opening of the blood-brain barrier and loading of bilirubin via intravenous administration. Clearance was rapid, with a half-time of 1.7 hours. This half time was the same as that for clearance of bilirubin from the serum, suggesting that brain bilirubin is removed by transport or diffusion back into the general circulation and does not bind to normal brain tissue. As bilirubin is rapidly cleared in the undamaged brain, its persistence in autopsy-proven neonatal kernicterus suggests that the latter disease is associated not only with bilirubin staining, but also with primary brain damage associated with fetal hypoxia. This work was done in collaboration with R. Levine (NHBLI).

2. Cerebrovascular permeability and transport.

a. Positron emission tomography and BBB integrity. Positron emission tomography was employed to examine time-dependent changes in blood-brain barrier permeability to $[68\text{Ga}]\text{EDTA}$ in the Rhesus monkey, following reversible barrier opening by intracarotid infusion of a hypertonic mannitol solution. The PET technique, when combined with measurements of plasma radioactivity, provided a quantitative measure of the cerebrovascular permeability-area product (PA) at different times after mannitol treatment. On the basis of these findings, the PET technique is being employed in patients with Alzheimer's disease and in age-matched controls to examine blood-brain barrier integrity. This work was conducted by N. Schlageter.

b. Pharmacokinetics of anticancer agent, melphalan. Melphalan, an anti-cancer alkylating agent with wide clinical use, was measured analytically by a high pressure liquid chromatography technique developed by D. Sweeney and N. Grieg, in brain and plasma. The pharmacokinetics of melphalan were determined in the rat, and parameters of protein binding analyzed in terms of whole blood melphalan and protein concentrations.

The cerebrovascular permeability-surface area product, PA, was determined for melphalan in awake rats, by N. Greig. This drug is transported by the carrier system that transports large neutral amino acids at the blood-brain barrier, consistent with melphalan being a derivative of phenylalanine. This system demonstrated saturation and competitive inhibition. Although the affinity of melphalan for the carrier is low, this study is the first that demonstrates that

a drug can enter the brain through facilitated transport, and suggests that drug design may allow entry of amino acid analogues that are therapeutically effective.

c. Glucose transport at BBB. P. Robinson developed a theoretical model that describes steady-state glucose transport into and utilization by the brain. The model takes into account cerebral blood flow, saturable transport of glucose across the BBB, and Michaelis-Menten kinetics for incorporation of glucose into the brain metabolic pool. The role of capillary heterogeneity is explicitly taken into account, and its effect on transport during hypoglycemia is analyzed. The model provides a quantitative analysis of glucose transport under normal and low-flow and hypoglycemic conditions.

d. Brain uptake of food dye, erythrocin B. It was demonstrated that erythrocin B does not enter the brain because of its very tight binding to plasma proteins, as proteins and their ligands are restricted by the blood-brain barrier. In vivo brain perfusion of protein-free fluid demonstrated that the dye can be taken up by brain by virtue of its lipid solubility. The dye, which is a food coloring agent and potentially neurotoxic, thus is prevented by acting on the brain in individuals with normal levels of blood proteins.

N. Transport Systems at the Blood-Brain Barrier

1. Method of analysis. A new in vivo brain perfusion method was developed by Q. R. Smith to quantitatively determine rates of facilitated and passive transfer of various solutes at the BBB. Unlike other current procedures, the method is free of errors caused by biotransformation in tissues other than brain, and makes it possible to accurately control the exact contents of the brain intravascular space. The method was employed to accurately measure maximum velocities of transport, and transport affinities, of a number of large neutral amino acids, and to further understand their role as precursors of neurotransmitters and proteins in the brain.

2. Relation of cerebrovascular permeability to solute lipid solubility. The brain perfusion method demonstrated a linear relation between cerebrovascular permeability of 22 nonelectrolytes and their octanol-water partition coefficients. Solute molecular weights ranged from 18 to 609 daltons. The relation is consistent with simple diffusion through an aporous lipid membrane and with the proposal of this laboratory that the endothelial layer of the blood-brain barrier corresponds to an extended lipid membrane with respect to drug penetration.

3. Facilitated transport of large neutral amino acids. Concentration-dependent uptakes into brain of eight large neutral amino acids were measured in anesthetized rats with the brain perfusion technique. Each uptake was stereospecific, saturable and sodium independent, and followed Michaelis-Menten kinetics with different affinities ($1/K_m$) and maximum velocities (V_{max}) for the different amino acids. There were no regional differences in K_m . The individual values K_m differed by 10-100 fold from values published by prior techniques. The correct calculation of affinities should make it possible to characterize the chemical structure of the amino acid carrier, for understanding regulation of transport into the brain.

4. Brain uptake of amino acids and aging in rats. The concentration dependent brain uptake of cycloleucine, a model nonmetabolizable large neutral amino acid, did not differ significantly between Fischer-344 rats aged 3 months and 24 months. The values for the Michaelis-Menten constants, K_m and V_{max} , also showed no significant difference. Lastly, the plasma concentrations of each of 9 neutral amino acids did not vary with age, except for a 50% increase in threonine in the old rats. Thus, contrary to previous reports, cerebrovascular transport of large neutral amino acids is age-invariant in the rats. As transport is coupled to brain protein synthesis, these findings support the finding by J. Cosgrove (see above) that brain protein synthesis is age-invariant in the rat. The work was done by Q. R. Smith.

5. Ionic homeostasis of the central nervous system.

a. Cerebrovascular permeability to ions. Homeostasis of ionic composition within the central nervous system is poorly understood in relation to aging and altered cerebral function. The transfer constants of a number of monovalent and divalent ions were measured at the blood-brain barrier of anesthetized rats by Q. Smith. It was shown that most rapid uptake from blood occurs by ion passage through the choroid plexus into cerebrospinal fluid, and not at the cerebral capillaries and directly into brain. Cerebrovascular permeabilities to ions are low, consistent with the continuous structure of the vascular endothelium. The study demonstrates multiple sites for ion exchange among brain, spinal fluid and blood.

b. Cerebrospinal fluid and capillary integrity in aging rats. Q. Smith showed that the rate of formation of cerebrospinal fluid (CSF) could be measured in rats by measuring CSF uptake of plasma ^{22}Na . No significant change in the rate occurred between 3 and 24 months of age in awake Fischer-344 rats, and a decrease of only 18% occurred by 34 months. Furthermore, a low capillary permeability to Na was maintained during aging of the rat. Therefore, with aging, the blood-brain barrier remains intact, and the rate of formation and turnover of CSF are unchanged in the rat.

c. Homeostasis of central nervous system calcium. Immature Fischer-344 rats were made hypo- or hypercalcemic by being fed diets that contained deficient or excessive amounts of calcium. After 8 weeks on the diets, plasma ionized and total calcium concentrations were 45% lower in low-Ca rats and 25% greater in high-Ca rats than in controls. In contrast, brain Ca changed by less than 9% and cerebrospinal fluid calcium changed by less than 13% in the experimental animals. The results demonstrate homeostasis of central nervous system calcium, and indicate that the blood-brain barrier must contain regulatory sites for calcium. This work was done by V. Murphy.

6. Analytical Methods and Pharmacokinetics.

1. Determination of the cholinergic agonist, arecoline. A method using gas-liquid chromatography with nitrogen-phosphorus detection was developed by J. N. Schreiber for the quantitative estimation in plasma and tissue samples of arecoline, a cholinergic agonist which is used clinically in the treatment of Alzheimer's disease. The method involves extraction of the compound from the biological matrix, followed by quantitation using the corresponding n-propyl ester as an internal standard.

2. Protein binding of drugs as affecting brain uptake. The blood-brain barrier is impermeant to proteins, so that binding of a drug or other biologically active substance to plasma proteins may hinder its entry into the brain. Changes in protein content and binding occur in aging and disease states. P. Robinson developed a mathematical model that describes quantitatively the binding of drugs to proteins, and that allows the prediction of brain uptake rates of protein-bound drugs. The model incorporates association and dissociation rate constants for the drug/protein complex, and relates them to regional cerebral blood flow and capillary transit time. The key factor determining drug uptake is the dissociation rate constant as compared to brain capillary transit time.

3. Development of analytical methods. Analytical methods using high performance liquid chromatography, with ultraviolet, electrochemical or fluorescent detection, were developed for the measurement of amines and esters of chlorambucil, an anticancer agent; amino acids in brain tissue; catecholamines and their metabolites in cerebrospinal fluid and plasma; amphotericin B in plasma and brain. This work was directed by D. Sweeney.

4. Pharmacokinetics of flurazepam (Dalmene). Flurazepam, a benzodiazepine, is one of the most commonly used narcotics used to induce sleep in the elderly. However, it frequently produces untoward long-term central nervous system effects, including hangover. A gas chromatographic-mass spectrographic procedure was developed to measure flurazepam and its metabolites, N1-desalkyl flurazepam and N1hydroxyethyl flurazepam. The pharmacokinetics of flurazepam and its metabolites then were determined after administration of the drug to the awake cat, in which metabolism of the drug is like that in humans. It was shown that N1-desalkyl flurazepam accumulated with time in the brain, and had an overall half-life of 50 hours in brain and blood. This accumulation probably explains the hangover and long-term neurotoxicity of this commonly used agent. This work was conducted by M. Chiueh.

P. Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems.

1. Age differences and relevance of extra-adrenal chromaffin tissue in rats. The LN previously demonstrated increased plasma concentrations of catecholamines in senescent Fischer-344 rats, but reduced responsivity of the cardiovascular and other systems to catecholamines. Increased concentrations may derive from paraganglia, extra-adrenal chromaffin tissue which are found in the para-aortic region of the rat and which are abundant in the fetus and at birth but degenerate postnatally. M. Partanen demonstrated that paraganglia proliferate in senescent Fischer-344 rats, and contain large quantities of catecholamines that probably contribute to high plasma levels. Growth of paraganglia may be an overall response of the sympathetic nervous system to reduced end organ sensitivity.

2. Age changes in human sympathetic ganglia. Sympathetic ganglia from human subjects aged 16 to 94 years, without neurodegenerative disorders, were obtained from sympathectomies or from autopsy. The lower cervical and upper thoracic (stellate) ganglia were processed for histochemistry and electron microscopy. Major age differences included: (1) decreased neuronal catecholamine histofluorescence, (2) increased autofluorescent lipopigment and heterogeneity of lipopigments, (3) dendritic hypertrophy. Some neurons demonstrated increased numbers of neurofilaments and neuropathological changes.

These findings establish baseline age changes in human sympathetic ganglia, for comparison with changes in disease states. The work was conducted by A. Hervonen.

Q. Synapse Development, Specificity and Mechanism in Culture.

1. J. W. Cosgrove and B. A. Suarez-Isla identified a protein fraction from medium conditioned from spinal cord neurons of chick embryos, which significantly decreases the percentage of muscle cells with slow hyperpolarizing after-potentials. These potentials also are decreased during synapse formation between spinal cord neurons and muscle cells. The results suggest that the protein fraction contains a critical element to the formation of long-lasting correct synapses.

2. Membrane properties of neurons of trisomic mouse. Trisomy 16 in mice is a model for trisomy 21 (Down syndrome) in humans, due to correspondence of specific trisomic genes. Experimental conditions were established to culture dorsal root ganglia from trisomic 16 mice and from control mice. It was demonstrated that trisomic neurons have a faster rate of rise of the action potential, and faster rate of fall of the action potential, than do controls, suggesting that trisomy 16 results in altered membrane currents associated with conduction and electrical activity. This work was done by C. Orozco.

R. Function of Peripheral Nerve and Muscle.

1. Hydraulic conductivity of nerve capillaries. The sciatic nerve of the frog was perfused in vivo with isotonic Ringer followed by Ringer made hypertonic by addition of sucrose or of NaCl. It was demonstrated that the nerve is elastic but has a low compliance, and that endoneurial capillaries have a low hydraulic conductivity. Due to the low permeability of endoneurial capillaries to small solutes such as NaCl and sucrose, furthermore, the nerve behaves as an osmometer. A low capillary hydraulic conductivity limits bulk water flow between blood and nerve, and a low compliance limits nerve swelling and edema. This work was conducted by S. Odman.

2. Facilitated transport of glucose from blood to nerve. Unidirectional influxes of radiotracers of D-glucose, L-glucose and 3-O-methyl-D-glucose across capillaries of rat tibial nerve were measured in situ, at different concentrations of perfusate D-glucose. The permeability-surface area product (PA) for the d-monosaccharides decreased, whereas the PA for L-glucose remained constant, when the concentration of unlabelled D-glucose in the perfusate was increased from 0 to 100 mM. The results demonstrate self-saturation, competitive inhibition and stereospecificity of glucose transport, and are consistent with facilitated transport of D-monosaccharides at nerve capillaries. This mechanism probably contributes to the resistance of the peripheral nerve to prolonged hypoglycemia, or to increased functional demand. This work was conducted by E. Rechthand.

3. Endoneurial capillary permeability to ^{14}C -sucrose in frog sciatic nerve. Using an in situ perfusion technique, the ^{14}C -sucrose permeability-surface area product (PA) was determined in endoneurial capillaries of the frog sciatic nerve. A low value was determined, consistent with a tight and intact blood-nerve barrier at nerve capillaries to water-soluble nonelectrolytes and to drugs. This work was performed by A. Weerasuriya.

4. Blood-nerve barrier permeability in experimental diabetes. Permeability-surface area (PA) products were determined with a quantitative in vivo injection technique at the blood-nerve barrier of the tibial nerve, and at the blood-brain barrier, of control and streptozotocin-induced diabetic rats. Using [^{14}C]-mannitol as a tracer, it was shown that permeability at the nerve was increased by 100% in diabetic animals compared with controls, but that permeability at the blood-brain barrier was unaltered in the diabetic animals. The increased permeability at the nerve was accompanied by a marked edema and a 32% decrease in conduction velocity. This study provides a possible pathophysiological explanation for the peripheral neuropathy that frequently accompanies diabetes mellitus in humans. This work was performed by E. Rechthand.

5. Innervation of the vasa nervorum. Using histofluorescence methods, periaxonal and arteriolar adrenergic nerves were shown to be present in the epineurium-perineurium of rat tibial nerve, suggesting that blood flow in the extrafascicular connective tissue is under neurogenic influence. In contrast, blood vessels in the nerve endoneurium were not associated with histofluorescent nerve fibers. These studies suggest that nerve blood flow regulation occurs in penetrating vessels and not within the confines of the blood-nerve barrier. This study was directed by E. Rechthand.

6. Nerve blood flow during hypotension. Laser Doppler flowmetry was employed to examine blood flow in sciatic nerves of barbiturate-anesthetized and unanesthetized decerebrate rats, in response to hypotension induced by graded exsanguination or by graded clamping of the descending aorta. Continuous flowmetry signals fell linearly with decreasing arterial blood pressure. In anesthetized as well as in unanesthetized rats, the signal approached zero at a systemic blood pressure of 14 mm Hg or less. The results do not demonstrate autoregulation of blood flow in the rat sciatic nerve during systemic hypotension. This work was conducted by T. Sundqvist.

7. Vesicular profiles in rapidly frozen nerves. Rapid freezing and freeze-substitution are procedures to identify intracellular structures and to avoid artifacts of tissue fixation. Using these techniques, it was demonstrated in the perineurium of the peripheral nerve, and in endothelial cells of the pia mater of frog brain, that vesicular structures which had been hitherto considered to be artifactual do indeed exist. As we have demonstrated that the vesicles do not contribute to transcellular transport, but are quite abundant in the barrier tissues, their role in organ function remains to be elucidated. This work was conducted by C. Latker.

8. Alkaline phosphatase in nerve and brain. C. Latker demonstrated alkaline phosphatase in different tissues of the blood-nerve barrier in frogs and rats, as well as in capillaries of the central nervous system of the rat. Within the perineurium of the frog sciatic nerve, for example, the enzyme is localized to caveoli or vesicular indentations, suggesting that these structures establish a restricted environment for transport regulated by this enzyme.

9. Blood-nerve barrier during Wallerian degeneration. Transection of the distal segment of the frog sciatic nerve results in degeneration of the axon. It was shown that the integrity of endoneurial capillaries which contribute to the blood-nerve barrier is altered for a period of up to 3 weeks following nerve

transection, with increased permeabilities to ^{14}C -sucrose and horseradish peroxidase. Thus, the presence of nerve tissue is critical to maintenance of bloodnerve barrier integrity, at least in the initial stages of Wallerian degeneration. This work was conducted by C. Latker and A. Weerasuriya.

S. Cellular Mechanisms During Regression of Blood Vessels.

Regression of blood vessels normally occurs in development, maturation and aging. It was shown that parenchymal blood vessels from the corpus luteum of the rabbit regress by dying off of endothelial cells, without eliciting a cellular infiltrate. The regressed cells appear to contribute to reorganization of the extracellular space by collagen and matrix. Regression, which also occurs in chondrogenic zones of digits of the chicken embryo, occurs prior to cartilage formation within the matrix. This work was performed by C. Latker.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00126-07 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Brain Function in Aging and Dementia		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	R. Friedland G. Berg C. L. Grady B. Horwitz M. Schapiro	Chief, SBAD Medical Staff Fellow Psychologist Senior Staff Fellow Medical Staff Fellow Others: S. I. Rapoport J. Haxby M. Sundaram Chief Staff Fellow Computer Aid
		LN, NIA MC, CC LN, NIA LN, NIA LN, NIA LN, NIA LN, NIA LN, NIA
COOPERATING UNITS (if any) Child Psychiatry Branch, NIMH Nuclear Medicine Department, Clinical Center, NIH University of Lund, Department of Clinical Neurophysiology, Lund, Sweden		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>The <u>regional cerebral metabolic rate for glucose (rCMRglc)</u> was examined as a measure of <u>cerebral functional activity</u> in 49 healthy men between the ages of 21 and 83 years. rCMRglc was determined by means of <u>positron emission tomography (PET)</u> with <u>18-F-2-fluoro-deoxy-D-glucose</u>, under <u>resting conditions</u>, when the subject's eyes were covered and his ears plugged to reduce sensory input. Average hemispheric glucose utilization in individual regions of the right and left hemispheres did not decline significantly with age ($p>0.05$), even after correction for <u>cerebral atrophy</u>. The constancy of cerebral glucose utilization with aging demonstrates the principle of homeostasis, and probably reflects redundancy and plasticity of the healthy senescent brain.</p> <p>rCMRglc was examined in patients with Alzheimer's disease. Absolute metabolic rates did not differ between mildly and moderately demented patients and controls, but ratios of metabolic rates to rCMRglc in the sensorimotor and occipital cerebral cortices showed reductions.</p> <p>Asymetry of cerebral metabolism in mildly and moderately demented patients was shown to be unchanged and correlated with appropriate neuropsychological deficits over periods of up to 2 years. Patterns of cerebral metabolism were demonstrated, using Q-component analysis in patients with Alzheimer's disease, and shown to characterize different patient groups unrelated to severity of dementia. Cerebral metabolism was assessed repeatedly in a 57 year old man</p>		
IRP-LN-391		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00136-03 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Functional Interactions Among Brain Regions in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: B. Horwitz Senior Staff Fellow LN, NIA
T. Soncrant Senior Staff Fellow LN, NIA

Others: C. Grady Psychologist LN, NIA
R. Duara Medical Staff Fellow LN, NIA
S. Sato Visiting Fellow LN, NIA
S. I. Rapoport Chief LN, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

.75

PROFESSIONAL:

.75

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A matrix method was developed to examine functional interactions between brain regions, by correlating the cerebral metabolic rate for glucose as determined by positron emission tomography in humans. The method was applied to regional metabolic data from 15 young and 15 older men. The method showed clear evidence of age differences, with older subjects having fewer significant correlations in frontal and parietal regions, indicative of reduced integrated activity in these regions with age. The correlation approach also was applied to 21 demented patients and 21 age-matched controls. The dementia group showed reduced frontal-parietal interactions, and a significant loss of correlations between left-right homologous regions.

The matrix method was applied to analyze glucose metabolism in awake Fischer-344 rats, and showed patterns of correlations similar to those in humans. Reduced correlations between left and right hemispheric brain regions were found in rats that had undergone corpus callosotomies, suggesting that interhemispheric interactions are mediated in part by callosal fibers.

IRP-LN-401

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00130-04 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neuropsychological Function in Aging and Dementia		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.V. Haxby G.L. Grady	Staff Fellow LN, NIA Staff Fellow LN, NIA
Others:	B. Sonies A. Cheng M. Rice	Speech Pathologist RM, CC Statistician LN, NIA Psychology Technician LN, NIA
COOPERATING UNITS (if any) Rehabilitation Medicine Department, Clinical Center Department of Psychology, Catholic University		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS: 2.4	PROFESSIONAL: 1.5	OTHER: 0.9
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> <u>Neuropsychologically relevant mental abilities are studied in healthy men at different ages, in patients with clinically-diagnosed Alzheimer's disease, and in adults with Down syndrome at different ages. Tests are administered to evaluate intelligence, memory, language, visual attention, visuoperceptive and visuoconstructive ability, and perceptual-motor speed. Age-related differences in general intelligence and visual memory in our sample of healthy men, ranging in age from 20 to 83 years, were found to be smaller than the differences reported in normative studies of non-health-screened adults. Visual memory and the discrepancy between verbal and visuospatial ability were not correlated with regional cerebral metabolic rates for glucose (rCMRglc) as measured by positron emission tomography (PET) and 18-Fluoro-deoxyglucose. Patients were divided into mildly, moderately and severely demented groups, based on the Mini-Mental State Examination. The discrepancy between verbal and visuospatial abilities was correlated with lateral asymmetry of cortical rCMRglc in patients with moderate Alzheimer's disease, but not in patients with mild Alzheimer's disease. Asymmetry of visual attention to the right and left sides of extrapersonal space was also related to lateral cerebral metabolic asymmetry in moderate Alzheimer's disease. Older Down syndrome adults perform worse on mental abilities tests than did younger subjects. Immediate verbal memory appears to be less affected by age in Down syndrome than are other abilities.</u> </p>		
IRP-LN-405		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00131-04 LN																
PERIOD COVERED October 1, 1985 to September 30, 1986																		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Neurological Function in Aging and Dementia																		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 10%;">PI:</td> <td style="width: 40%;">C.L. Grady</td> <td style="width: 30%;">Psychologist</td> <td style="width: 20%;">LN, NIA</td> </tr> <tr> <td>Others:</td> <td>A. Grimes</td> <td>Audiologist</td> <td>CC</td> </tr> <tr> <td></td> <td>A. Pikus</td> <td>Audiologist</td> <td>CC</td> </tr> <tr> <td></td> <td>J.W. Renfrew</td> <td>Psychologist</td> <td>LN, NIA</td> </tr> </table>			PI:	C.L. Grady	Psychologist	LN, NIA	Others:	A. Grimes	Audiologist	CC		A. Pikus	Audiologist	CC		J.W. Renfrew	Psychologist	LN, NIA
PI:	C.L. Grady	Psychologist	LN, NIA															
Others:	A. Grimes	Audiologist	CC															
	A. Pikus	Audiologist	CC															
	J.W. Renfrew	Psychologist	LN, NIA															
COOPERATING UNITS (if any) Audiology, Clinical Center																		
LAB/BRANCH Laboratory of Neurosciences																		
SECTION Brain Aging and Dementia																		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892																		
TOTAL MAN-YEARS: .6	PROFESSIONAL: .3	OTHER: .3																
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) <p>Research was carried out on <u>motor function in man</u> in relation to <u>aging</u>. With the use of a <u>patient activity monitor</u> worn on the non-dominant wrist in 43 healthy men for a period of 9 days, it was demonstrated that average motor activity was lower in older individuals, primarily as a result of low activity during daytime hours. Weekend mean activity was significantly different than weekday mean activity only in the younger subjects as a result of young subjects sleeping later on weekends than during the weekday period.</p> <p>In patients with Alzheimer's disease, studies of <u>central auditory function</u> using both <u>dichotic</u> and <u>degraded monotic tests</u> showed that performance on the dichotic test was more difficult for the patients, compared to healthy controls. In addition, only dichotic performance was related to measures of <u>cerebral atrophy</u> and <u>glucose metabolism</u> in the <u>temporal lobes</u>.</p>																		
IRP-LN-412																		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00403-01 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Genetics of Alzheimer's Disease		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	A. Moore E. Koss M. Schapiro	Social Worker Staff Fellow Senior Staff Fellow Neurologist
		LN, NIA LN, NIA LN, NIA Univ. of Maryland
Others:	S.J. Kittner	
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.2	.3
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A dementia clinic was maintained to evaluate patients for in-patient and out-patient protocols. One-hundred and fifty five patients were diagnosed with various batteries as having <u>primary degenerative dementia</u> , <u>multi-infarct dementia</u> , and other dementias. The <u>Hachinski Ischemic Score</u> distinguished vascular from non-vascular dementias, whereas other dementias scores were not discriminatory. <u>Pedigrees were constructed from family history of all patients participating in the dementia program, to examine the genetic basis of Alzheimer's disease.</u>		

IRP-LN-418

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00132-04 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.) Brain Anatomy in Aging and Dementia		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: J. Luxenberg Medical Staff Fellow LN, NIA Others: R. Friedland Section Chief LN, NIA S.I. Rapoport Laboratory Chief LN, NIA H.A. Fredericks Electrical Engineer CSL, DCRT J. Rumsey Psychologist LNC, NIMH J. Kaye Medical Staff Fellow LN, NIA M. Schapiro Medical Staff Fellow LN, NIA H. Creasey Medical Staff Fellow LN, NIA		
COOPERATING UNITS (if any) Computer Systems Laboratory, Division of Computer Research Technology Laboratory of Child Psychiatry, MINH		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS 1.3	PROFESSIONAL: 1.3	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> <u>Computer assisted tomography (CT)</u>, together with three dimensional image reconstruction procedures, in patients with <u>dementia of the Alzheimer type (DAT)</u>, demonstrated that the volume of <u>cerebrospinal fluid</u> was larger than in age and sex matched control subjects, and that the volume of <u>gray matter</u> was smaller. <u>Ventricular enlargement</u> in the male DAT patients corresponds to the severity of <u>dementia</u>. In healthy subjects, men had larger volumes of cerebrospinal fluid in third and lateral ventricles than did women. Volumetric CT analysis demonstrated no differences, as compared with age matched controls, in <u>brain morphometrics</u> for adults with autism and for young adults with Down syndrome (after data were normalized to body height). </p> <p> In male DAT patients, mean rates of enlargement of <u>third ventricle</u> volume and of total lateral ventricular volumes differed significantly from zero and from respective control values. There was no overlap between the rates of lateral ventricular enlargement in patients and controls. The rate of neuropsychological decline correlated with the rate of enlargement of the third ventricle and the right lateral ventricle. </p>		
IRP-LN-422		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00140-02 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cerebrospinal Fluid Chemistry in Aging and Dementia		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	C. May J.R. Atack	Medical Staff Fellow Visiting Associate LN, NIA LN, NIA
Others:	M. Schapiro	Medical Staff Fellow LN, NIA
COOPERATING UNITS (if any) Laboratory of Neurochemistry, NIMH Department of Pharmacology, University of Pittsburgh, School of Medicine Department of Endocrinology, Johns Hopkins School of Medicine Biological Psychiatry Branch, NIMH - Clinical Pathology Department, CC		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia/Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS 1.4	PROFESSIONAL: 1.4	OTHER:
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.) <u>Cerebrospinal fluid concentrations of homovanillic acid, 5-hydroxy-indoleacetic acid, norepinephrine and 3-methoxy 4-hydroxyphenyl-ethylene glycol</u> did not differ significantly between patients with <u>Alzheimer's disease</u> and age matched controls, and were not correlated with age in healthy men. Spinal fluid concentrations of <u>choline</u> increased with age in healthy men, and were higher in young adults with <u>Down syndrome</u> than in age matched controls. <u>CSF bioperin</u> , a coenzyme for tyrosine and tryptophan hydroxylase, was lower in patients with Alzheimer's disease than in controls, and was correlated with concentrations of 5-hydroxy-indoleacetic acid and <u>homovanillic acid</u> . <u>Corticotropin releasing factor</u> , a neuropeptide, was significantly reduced in the cerebrospinal fluid of patients with Alzheimer's disease as compared to controls, as was <u>peptidyl-alpha-amidation</u> activity, suggesting a loss of <u>neurons</u> which produce amidated neuropeptides. Ratios of <u>albumin</u> and <u>immunoglobulin</u> between cerebrospinal fluid and plasma were normal in Alzheimer's patients, suggesting that the <u>blood brain barrier</u> is intact. Neuron-specific enolase, a glycolytic enzyme enolase, was significantly reduced in cerebrospinal fluid of patients with Alzheimer's disease.		
IRP-LN-426		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00133-04 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Clinical Pharmacokinetics, Pharmacodynamics and Therapeutics		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J. Kaye	Medical Staff Fellow LN, NIA
Others:	P.K. Narang	Staff Fellow PHARM, CC
	L. Lesko	Consultant to NIH, CC Pharm PHARM, CC
	M. Power	Staff Nurse Nursing, CC
	M. Ninos	Staff Nurse Nursing, CC
	N.R. Cutler	Section Chief (former) LN, NIA
COOPERATING UNITS (if any) Pharmacy Department, Clinical Center		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Brain Aging and Dementia		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.4	.4	.0
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.) <p>Vancomycin's half life of the terminal phase is significantly prolonged in the elderly compared to young normals. No significant change was observed in <u>volume of distribution</u> which could be accounted for by altered tissue binding.</p> <p>Zimelidine, a <u>serotonergic reuptake blocker</u>, was evaluated in Alzheimer's disease patients. Pharmacokinetic, neurochemical and neuropsychological effects were examined. The drug significantly reduced (by up to 38%) <u>5-hydroxy-indolacetic acid concentrations</u> in cerebrospinal fluid (CSF). CSF concentrations of <u>3-methoxy-4-hydroxy-phenylglycol</u>, a major metabolite of norepinephrine, tended to increase slightly. Overall, there was no effect of zimelidine on memory function.</p>		
IRP-LN-432		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00125-08 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cerebral Metabolism, Relation to Brain Function and Aging		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> PI: T. Soncrant G. Ricchieri E. McCann </div> <div style="width: 30%;"> Staff Fellow Visiting Fellow Medical Staff Fellow </div> <div style="width: 30%;"> LN, NIA LN, NIA LN, NIA </div> </div>		
COOPERATING UNITS (if any) Department of Neuropathology, University of Western Ontario, Canada		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS: 5.0	PROFESSIONAL: 3.0	OTHER: 2.0
CHECK APPROPRIATE BOX(ES) <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews </div> <div style="width: 30%;"> <input type="checkbox"/> (b) Human tissues </div> <div style="width: 30%;"> <input checked="" type="checkbox"/> (c) Neither </div> </div>		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>The regional cerebral metabolic rate for glucose ($rCMR_{glc}$) was examined in awake Fischer-344 rats in relation to age, pharmacological stimulation and behavior. The lumped constant used to calculate $rCMR_{glc}$ was shown to decline with age in Fischer-344 rats.</p> <p>Arecoline, a cholinergic agonist, stimulated $rCMR_{glc}$ in a number of brain regions, including those with muscarinic receptors. Cerebral metabolic responses were not reduced in senescent animals, indicating maintenance of postsynaptic cholinergic function. Metabolic responses to nicotine, another cholinergic agonist, were consistent with the distribution of nicotinic receptors within the rat brain.</p> <p>Dopaminergic function in the rat brain was examined by measuring $rCMR_{glc}$ in response to haloperidol (a dopaminergic antagonist), bromocriptine (an agonist) and sulpiride (a specific antagonist). The response to haloperidol was reduced in senescent as compared to younger rats, despite higher concentrations of haloperidol in the older animals, suggesting a reduced central dopaminergic function, and an imbalance between the cholinergic and dopaminergic systems in the brain of the senescent rat. Metabolic responses to haloperidol depended on time after treatment, and demonstrated tolerance after long-term administration.</p> <p>Regional cerebral blood flow (rCBF) was age invariant in awake Beagles between 1 and 12 years, and declined only in extreme senescence in relation to systemic disease, suggesting that cerebral functional activity is maintained during the life span of the healthy Beagle.</p>		
IRP-LN-441		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00134-03 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Brain Lipid Metabolism, Relation to Function and Aging		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J. Gnaedinger	Staff Fellow LN, NIA
	J. Miller	Staff Fellow LN, NIA
Others:	P. Robinson	Visiting Associate LN, NIA
	O. Tone	Visiting Fellow LN, NIA
	J. Bell	Chemist LN, NIA
	D. Sweeney	Chemist LN, NIA
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.75	3.50	1.25
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>A method was developed to measure the rate of incorporation of <u>palmitate</u> from plasma into different <u>brain regions</u> in the awake rat, Jpalm. Furthermore, a <u>theoretical model</u> was developed to calculate Jpalm from data, and to interpret the results.</p> <p>Jpalm did not change with <u>aging</u> in Fischer-344 rats between 3 and 34 months of age, indicating that the rate of <u>turnover of palmitate-containing brain lipids</u> was unchanged. During development of the rat, Jpalm increased between 15 and 20 days, then fell more than 8 fold to maturity. The time course corresponded to the time course of <u>myelination</u> in the developing brain.</p> <p>Jpalm was found to fall in the pituitary and pineal glands of Brattleboro rats as compared to controls, and to fall in central <u>auditory pathways</u> following damage to the <u>cochlea</u> of rats.</p>		

IRP-LN-454

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00135-03 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Gene Expression in Brain: Aging and Dementia		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J.W. Cosgrove	Senior Staff Fellow LN, NIA
Others:	J.R. Atack M. Matocha	Visiting Fellow Staff Fellow LN, NIA LN, NIA
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unspaced type. Do not exceed the space provided.) Amino acid incorporation was measured in a cell-free protein synthesis system derived from the brains of male Fischer-344 rats of different ages. This system has the capacity to initiate protein synthesis in vitro. There was no significant correlation between protein synthesis and age. Analysis of neurofilament proteins in the rat central nervous system by two dimensional gel electrophoresis revealed the three neurofilament proteins of 210, 160, and 68K daltons. Heterogeneity existed in the protein pattern, especially in the 68K daltons polypeptide. Analysis of gene expression in 11 individual regions of the rat brain at the level of protein end-product was conducted using two dimensional gel electrophoresis in conjunction with a sensitive silver stain protein detection procedure. Differential gene expression was observed for a number of brain proteins, but the level of most brain proteins did not change with age. The levels of mRNA associated with the translational apparatus in 3 regions of the rat brain was studied using two dimensional gel electrophoretic analysis of the radiolabeled products of in vitro translation of brain free and membrane bound polyribosomes. Differential gene expression was observed for a number of brain messenger RNAs. The majority of brain messenger RNAs in the three brain regions did not change with age. Levels of the cellular homologue of the Rous sarcoma virus, c-src, were examined in rat brain as a function of age, using Northern blotting and nucleic acid hybridization and immunoprecipitation of translation products. The levels of expression of c-src are age invariant in the rat brain.		
IRP-LN-461		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00127-06 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Brain Markers in Aging and Dementia (Assmt. of Neuroch. Markers in Rel. Age B/D)		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	J. Attack D. Mochlin	Visiting Fellow Neuropathologist LN, NIA LN, NIA
Others:	C. Fiori D. Katz M. Ball	Physical Scientist Pathologist Neuropathologist BEIB, NIH CC, NIH Univ. W. Ontario,
COOPERATING UNITS (if any) Biomedical Engineering and Instrumentation Branch, NIH. Department of Neuropathology, University Western Ontario, Canada.		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Rats made diabetic by administration of streptozotocin showed decreases in the activity of tyrosine hydroxylase, and increased concentrations of norepinephrine, in various brain regions, including the <u>thalamus</u> and <u>hypothalamus</u>. These results suggest that diabetes can alter brain <u>monoamine metabolism</u> and behavior subserved by <u>monoamine neurotransmitters</u>.</p> <p>Procedures were established to obtain rapid autopsies on inpatients and outpatients who die, and for preparing <u>brain tissue</u> for diagnosis and chemical and neurochemical analysis.</p>		
IRP-LN-466		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 0120-09 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Blood-Brain Barrier and Central Nervous System Function		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	S.I. Rapoport M.H. Greig D.J. Sweeney	Chief Visiting Associate Chemist Neurosurgeon Visiting Fellow Biologist
		LN, NIA LN, NIA LN, NIA Tokyo, Japan LN, NIA LN, NIA
Others:		
	S. Sato J. Kusmierz B.K. Armstrong	Tokyo, Japan LN, NIA LN, NIA
COOPERATING UNITS (if any)		
Laboratory of Biochemistry, NHLBI		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither		
<input type="checkbox"/> (a1) Minors		
<input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
<p>Melphalan, an anticancer alkylating agent, was measured in the blood and brain of rats and its <u>pharmacokinetics</u> determined. It enters the brain via an <u>amino acid transport system</u> at the blood-brain barrier; its entry is related to its <u>plasma protein binding</u>, which is <u>concentration-dependent</u>.</p> <p>The blood-brain barrier was not affected by <u>dimethyl sulfoxide</u>, but could be opened in rats and mice by intracarotid infusion of a hypertonic arabinose solution. The rate of reclosure was related to the size of the intravascular tracer, indicating that tight junctions between cerebrovascular endothelial cells were modified. Reversible osmotic barrier opening was used to deliver <u>interferon</u> to the brain of rats.</p> <p>A mathematical model for uptake and metabolism of glucose by brain was developed and used to interpret glucose transport during <u>hypoglycemia</u> and <u>hyperglycemia</u>.</p> <p>Brain uptake of the food dye <u>erythrosin B</u> is restricted by its binding to plasma protein, and not by its impermeability at the blood-brain barrier.</p> <p>Bilirubin was allowed into the brain of rats following osmotic opening of the blood-brain barrier, and shown to have a cerebral half-time of 1.7 hours. Retained bilirubin in <u>human kernicterus</u> therefore probably reflects <u>neonatal brain damage</u>.</p>		
IRP-LN-470		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00129-05 LN																					
PERIOD COVERED October 1, 1985 to September 30, 1986																							
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Transport Systems at the Blood-Brain Barrier																							
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: Q. R. Smith</td> <td style="width: 33%;">Physiologist</td> <td style="width: 33%;">LN, NIA</td> </tr> <tr> <td>V. Murphy</td> <td>Staff Fellow</td> <td>LN, NIA</td> </tr> <tr> <td>M. Aoyagi</td> <td>Visiting Fellow</td> <td>LN, NIA</td> </tr> <tr> <td colspan="3" style="padding-top: 10px;">Others: S.I. Rapoport</td> </tr> <tr> <td>D. Sweeney</td> <td>Chief</td> <td>LN, NIA</td> </tr> <tr> <td>T. Nagashima</td> <td>Chemist</td> <td>LN, NIA</td> </tr> <tr> <td></td> <td>Visiting Fellow</td> <td>LN, NIA</td> </tr> </table>			PI: Q. R. Smith	Physiologist	LN, NIA	V. Murphy	Staff Fellow	LN, NIA	M. Aoyagi	Visiting Fellow	LN, NIA	Others: S.I. Rapoport			D. Sweeney	Chief	LN, NIA	T. Nagashima	Chemist	LN, NIA		Visiting Fellow	LN, NIA
PI: Q. R. Smith	Physiologist	LN, NIA																					
V. Murphy	Staff Fellow	LN, NIA																					
M. Aoyagi	Visiting Fellow	LN, NIA																					
Others: S.I. Rapoport																							
D. Sweeney	Chief	LN, NIA																					
T. Nagashima	Chemist	LN, NIA																					
	Visiting Fellow	LN, NIA																					
COOPERATING UNITS (if any)																							
LAB/BRANCH Laboratory of Neurosciences																							
SECTION Cerebral Physiology and Metabolism																							
INSTITUTE AND LOCATION NIA, NIH, Bethesda, MD 20892																							
TOTAL MAN-YEARS <div style="text-align: center;">3.0</div>	PROFESSIONAL <div style="text-align: center;">3.0</div>	OTHER <div style="text-align: center;">0</div>																					
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews																							
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Transport mechanisms at the <u>blood-brain barrier</u> were studied in the rat. Barrier permeability to <u>nonelectrolytes</u> was linearly related to lipid solubility. Large neutral amino acids cross the blood-brain barrier by <u>facilitated diffusion</u>. The affinity of the cerebrovascular transport system for amino acids is 10-100 fold greater than amino acid transport systems in other tissues, and makes the brain susceptible to imbalances in plasma amino acid concentrations. Cerebrovascular transport of large neutral amino acids did not change significantly in the <u>Fischer-344 rat</u> between 3 and 24 months of <u>age</u>.</p> <p>The cerebrovascular permeability to inorganic ions was low, comparable to a cell membrane, and followed the sequence $K > Mg > Na > Cl > Ca$. The low permeability of the cerebrovascular endothelium to Na was maintained with <u>age</u> in the rat, and the <u>cerebrospinal fluid</u> transfer constant for Na fell by only 18%.</p> <p>Calcium influx into the brain was directly proportional to the plasma concentration of ionized calcium. Ca concentrations in brain and CSF were maintained within 13% of control values during chronic changes of up to 50% in plasma Ca concentration. Ca homeostasis is consistent with <u>active, regulated transport</u> of Ca at the blood-brain barrier.</p>																							

IRP-LN-480

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00123-06 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Analytical Methods and Pharmacokinetics (Drug Pharmacokinetics, Relation to Pharmacodynamics and Senescence)		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	D. Sweeney P. J. Robinson	Chemist Visiting Associate LN, NIA LN, NIA
Others:	E. Daly J. Kusmierz S. I. Rapoport E. A. Neuwelt	Chemist Visiting Fellow Chief Neurosurgeon LN, NIA LN, NIA LN, NIA Org Hlth Sci Ctr
COOPERATING UNITS (if any) Department Neurosurgery, Oregon Health Sciences Center		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
1.5	1.0	0.5
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Analytical methods using <u>high performance liquid chromatography, with ultra-violet, electrochemical or fluorescent detection</u> , were developed for the <u>measurement of (1) of amides and esters of chlorambucil an anticancer agent; (2) amino acids in brain tissue; (3) catecholamines and their metabolites in cerebrospinal fluid (CSF) and plasma; (4) amphotericin B in plasma and brain; (5) polyols in cerebrospinal fluid and plasma.</u> A gas chromatographic-mass spectrometric procedure was developed to measure <u>flurazepam (Dalmane) and its metabolites, N1-desalkyl flurazepam and N1-hydroxyethyl flurazepam.</u> The long term accumulation of <u>N1-desalkyl flurazepam</u> in the cat brain, after administration of flurazepam, probably explains hangover and long term neurotoxicity of this sleep medicine in the elderly. A model was developed to interpret <u>drug binding to plasma proteins</u> as regulating the rate of drug entry into brain from blood.		
IRP-LN-486		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00122-08 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	A. Hervonen Others: J. E. Johnson, Jr. M. Partanen	Visiting Scientist Expert Visiting Fellow LN, NIA EM, NIA LN, NIA
COOPERATING UNITS (if any) Section of Gerontology, Departments of Biomedical Sciences and Public Health, University of Tampere, Finland.		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS: 0.6	PROFESSIONAL: 0.6	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Activities of tyrosine hydroxylase, dopamine beta hydroxylase and choline acetyltransferase were examined in sympathetic ganglia of Fischer-344 rats at different ages. Increased activities of some of these enzymes were noted in the superior cervical ganglia, adrenal glands and hypogastric ganglion of older rats, suggesting enhanced neurotransmitter synthesis with age. Age changes in catecholamine histofluorescence and lipopigment autofluorescence in sympathetic ganglia from the rat and from humans.		
IRP-LN-490		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00123-08 LH
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.) Neuronal Development in Tissue Culture		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	C. Orozco K. Nieminen	Visiting Fellow LN, NIA Visiting Fellow LN, NIA
Others:	J.W. Cosgrove B.A. Suarez-Isla	Senior Staff Fellow LN, NIA Visiting Associate LN, NIA
COOPERATING UNITS (if any) Salk Institute, LaJolla, CA Department of Neurobiology, University of Illinois Department of Pediatrics, University of California		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS: 3.0	PROFESSIONAL: 2.5	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input checked="" type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Membrane channels in the sarcoplasmic reticulum of striated skeletal muscle were shown to be selective for calcium using a <u>patch clamp technique</u>, and to have a voltage dependent conductance.</p> <p>Spinal cord neurons cocultured with muscle cells induce a decrease in the incidence of <u>slow hyperpolarizing after potentials</u> following an overshoot of the action potential. A <u>soluble factor</u> released by these neurons, and causing this effect, was isolated, with a molecular weight of less than 4000 daltons.</p> <p>Dorsal root ganglia neurons from trisomy 16 mice, a model for trisomy 21 (<u>Down syndrome</u>) in humans, were maintained in tissue culture, and show to have different <u>electrical properties</u> than control neurons.</p>		
IRP-LN-494		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00121-09 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Function and Structure of Peripheral Nerve		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI:	E. Rechthand C. Latker	Senior Staff Fellow Senior Staff Fellow LN, NIA LN, NIA
Others:	S. Sato K.C. Wadwhani T. Sundqvist P. Robinson	Investigator Student Investigator Investigator Visiting Associate Univ. of Kieo LN, NIA Univ. of Linkoping LN, NIA
COOPERATING UNITS (if any) Univ. of Kieo, Tokyo; Univ. of Linkoping, Sweden; SUNY State Univ., New York; Univ. of Maryland, MD; Key Pharmaceuticals, Miami; Univ. of Colombo, Sri Lanka; US Uniformed Health Services, Bethesda, MD.		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	3.5	1.0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p>Glucose transport into the rat tibial nerve from blood, across blood vessels of the nerve endoneurium, is by a facilitated transport system that demonstrates <u>stereospecificity</u> and <u>saturation</u>, and allows matching of transport and nerve metabolic demand.</p> <p>Permeabilities of the blood-nerve barrier to ions and nonelectrolytes are low, indicating limited exchange between blood and nerve. However, the barrier does not regulate nerve calcium, which slowly equilibrates between nerve and blood during chronic <u>hypocalcemia</u> and <u>hypercalcemia</u>. Capillaries of the nerve vasculature become more permeant during <u>experimental diabetes</u>, resulting in a <u>peripheral neuropathy</u> in rats accompanied by <u>nerve edema</u>.</p> <p><u>Blood flow</u> in the rat sciatic nerve, as measured with laser doppler flowmetry, does not seem to be autoregulated during acute hypotension. Histofluorescence methods indicate <u>adrenergic innervations</u> of blood vessels on the surface of the nerve, but not neuronal innervation within the nerve endoneurium.</p> <p>Vesicular profiles are demonstrated in the perineurium of frog nerve and in endothelial cells of pial blood vessels, using rapid freezing and freeze substitution methods, demonstrating that vesicles do not contribute to transcellular macromolecular transport. <u>Alkaline phosphatase</u> within vesicles indicate that they are microdomains for enzymatic activity. <u>Wallerian degeneration</u> alters the permeability of the blood nerve barrier tissues of the frog for up to 6 weeks.</p>		
IRP-LN-498		

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00400-01 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Mechanisms of Blood Vessels Regression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. Latker Senior Staff Fellow LN, NIA

Others: R. Feinberg Assistant Professor N.J. Univ. of Med. and Dent.
D. Beebe Associate Professor USUHS
M. Koering Professor George Washington Univ. Med.

COOPERATING UNITS (if any)

N.J. University of Med. and Dent., New Jersey; USUHS, Bethesda, Maryland; George Washington University of Medicine, Washington, D.C.

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

1.0

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Endothelial cells, in blood vessels which normally regress in a nonlytic manner. Early involution involves hypertrophy of endothelial cells followed by a late cellular shrinkage. In some developmental systems in which vascular regression is normal, some of the endothelial cells appear to transdifferentiate into other cell types.

IRP-LN-507

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00402-01 LN
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.) Neuroplasticity and the Progression of Neurogenerative Disorder		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: B. Horwitz Senior Staff Fellow LN, NIA		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Neurosciences		
SECTION Cerebral Physiology and Metabolism		
INSTITUTE AND LOCATION NIA, NIH, Bethesda, Maryland 20892		
TOTAL MAN-YEARS .25	PROFESSIONAL: .25	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)		
<p> A neurobiological hypothesis is proposed to explain the relation between the percentage cell loss in the cholinergic basal forebrain and the density of neuritic plaques in cortex in Alzheimer's disease: When cells in the cholinergic basal forebrain die, their cortical synaptic target sites can be reoccupied by axonal sprouting of other neurons from the basal forebrain. This neuroplasticity hypothesis leads to equations that are consistent with the quantitative data, and it makes specific predictions that can be tested experimentally. Moreover, this hypothesis suggests that the more rapid course of the presenile form of Alzheimer's disease and its more extensive pathology can be understood as a consequence of the <u>decline in neuroplasticity with age.</u> </p>		
IRP-LN-511		

Annual Report of the Laboratory of Personality and Cognition

National Institute on Aging

Overview

This is the inaugural Annual Report of the Laboratory of Personality and Cognition (LPC) created in FY86. The fundamental scientific paradigm which unites and guides research in the laboratory is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ--in health, in rates of aging, in cognitive ability, in personality, in happiness and life satisfaction. The mission of LPC is threefold: (1) to conduct basic and clinical research on individual differences in cognitive and personality processes and traits; (2) to investigate the influence of age on these variables and their reciprocal influence on health, well-being and adaptation; and (3) to employ longitudinal, experimental and epidemiological methods in the analysis of psychological and psychosocial issues of aging including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

Individual Differences in Adaptation

LPC's emphasis on the importance of research on individual differences in personality and intellectual functioning is based on theoretical conviction and empirical evidence, both of which demonstrate their influence on health and adaptation. For instance, basic research on personality dispositions have led Laboratory scientists to formulate a model of individual differences in psychological well-being which clarifies and extends understanding of such processes as morale, life satisfaction and happiness. The phenomena subsumed by the model have long preoccupied scientists and gerontologists interested in successful aging, and, moreover, are crucial to explanations of adaptation.

Stability of Psychological Well-Being

Even though it is only one of the components of quality of life, psychological well-being is of great intrinsic interest and serves as an important indicator of the subjective experience of aging. Questions regarding whether old age is as bleak a period as younger people commonly assume and whether there is an emotional blunting with age can be answered with data from a longitudinal followup of a national sample. Data from the NHANES I Epidemiologic Followup Study, a multistage, stratified probability sample of the noninstitutionalized civilian population of the USA, give clear evidence that psychological well-being does not decline with age. When retested after 9 years there was no change in the average level of well-being for 4,942 men and women initially aged 25-75.

Independence of Life Changes and Happiness

Further, the data showed that people who initially scored high in well-being continued to score high on retest, that psychological well-being was equally stable in men and women, and that these individual differences were preserved even when respondents had experienced changes in marital status, employment status and state of residence. How happy or unhappy an individual will be a decade later can be predicted with some accuracy and the prediction of future happiness can be made far more accurately from measures of past happiness than from such significant life circumstances as marital status, sex, race, or age. Changes in marriage, work and residence apparently have little influence on the prediction of well-being, at least over the interval of a decade. Stability is thus attributable to enduring dispositions in the individual rather than to continuities in these life circumstances.

Not only do these findings provide compelling evidence for the stability of levels of well-being in adulthood, but they also rebut negative stereotypes of aging which depict the later years as a time of depression and dejection, wherein poor health, in particular, takes its toll on well-being. Specifically, a Health Concern subscale of the Well-being measure showed no significant age changes over the same ten year interval, despite the frequency of documented health changes with age. The findings from this national followup sample that aging is not associated with increased worry or concern about health is consistent with previous longitudinal findings from the BLSA and provide striking support for the view that aging individuals are not hypochondriacs (Costa and McCrae, 1985). It remains to be seen whether changes in health status influence subsequent well-being. Life threatening conditions such as cancer, heart disease, and disabilities that force major alterations in life-style, might significantly influence well-being. This line of investigation is an important priority for the coming year.

Generalizability of Findings

It should be noted that the NHANES I Followup data both supplement and extend the limits of the research topics that can be investigated in the (Baltimore Longitudinal Study of Aging) data. The findings on psychosocial continuity, including personality stability and psychological well-being, that have emerged from the BLSA have been subject to the objection that the volunteer participants of the BLSA, as well as other longitudinal studies, do not form a representative sample, and that age differences or changes in personality and well-being may be more common in the general population. But the analyses and results stemming from the NHANES I Followup confirm the absence of age effects. As a whole these results lend much confidence in the conclusions derived from longitudinal studies such as the BLSA.

Understanding Aging

One of the most important applications of the basic and clinical research of Laboratory of Personality and Cognition is in understanding and characterizing psychological aging. LPC and its investigators continue to make a heavy investment in time and resources in the Baltimore Longitudinal Study of Aging. LPC research has led to increased attention and understanding of the individuality and specificity of aging processes. Recognition of this great diver-

sity is of vital importance in gaining an accurate picture of the varied psychological and behavioral performance of aging individuals. In addition to describing what does and does not change and how much of a change there is with age, another important focus involves disentangling the effects of disease and illness from maturational and aging processes. During the past year, LPC investigators have made important contributions to describing the patterns of age changes in cognitive performance, including problem-solving or reasoning performance, memory and learning performance, vigilance-sustained attention performance, divergent thinking or creativity performance; self-perceptions of health; and psychological well-being. We turn to brief highlights of these new findings regarding age changes:

Continuity and Change in Cognition

One of the longest-held truisms about continuity and change in cognitive dimensions holds that individuals' general fund of knowledge, as indexed by vocabulary test performance, does not decline with aging. Results from 12 and 18 year longitudinal changes in WAIS vocabulary performance of men in the BLSA indicated statistically significant though small declines for the men initially in their sixties and seventies. The decline in vocabulary test performance amounts to about 5% of the total over a 12 year period. A related finding involved longitudinal analyses of age changes in nonverbal memory performance, which employed individual regression measures of change on the Benton Visual Retention Test (BVRT), showed substantial mean declines for the groups of men initially 60 and 70.

Divergent thinking ability is the ability to produce a variety of acceptable solutions to a problem and has been thought to underlie creativity. Longitudinal data gathered from 1959 to 1972 on 6 measures from over 800 men in the BLSA covering the age range from 17 to 101 showed that performance on divergent thinking tests improves until about age 40 and declines thereafter. Although consistent, age was not a particularly powerful predictor of creativity performance. Rather, individuals showed great consistency over a 6-year period in their rank order. These data suggest that individuals high in divergent thinking characteristics are likely to remain relatively high for most of their adult years.

Although aging is an important influence on cognitive processes and performance, its effects are by no means universal. Other longitudinal results obtained this year involving sustained attention on vigilance tests with no memory demands and using infrequent target occurrence (i.e., only 23 times per hour) demonstrate that the ability to perform such pure vigilance tasks does not decline significantly with age, suggesting, perhaps, that contrary to prevailing wisdom, older individuals can perform jobs requiring vigilance, such as industrial inspection and watchkeeping, as well as younger persons.

Effects of Aging and Disease

In addition to charting the patterns of age changes, another major research objective of LPC is to disentangle the effects of aging from disease and associated medical conditions on various cognitive and personality performances. Many declines associated with age are due not to aging per se but to illnesses associated with age (secondary aging). One particular disease thought to acce-

lerate cognitive aging or age declines in cognitive performance is diabetes. The onset of type II or noninsulin dependent diabetes is usually after age 40. Six and twelve-year longitudinal comparisons between type II diabetics and age and education-matched controls found no effect on nonverbal memory performance (BVRT) and general intelligence--WAIS vocabulary changes. In contrast to published cross-sectional results which suggested that diabetes accelerated cognitive aging, no evidence was obtained from longitudinal analyses to support that hypothesis. Aging, but not disease, type II diabetes in this instance, was found to influence declines in cognitive performance. Thus, not only is aging distinct from disease, but the respective effects of each are also distinct and, it should be noted, specific.

Another example of the lack of effect of a physiological condition or variable on psychological processes is given by the finding this year that hypertensive status of men and women in the BLSA, as measured by basal blood pressure determinations, had no influence on perceptions of health, although a small effect for history of drug treatment--interpreted as a "labelling" effect--was found.

Applications of Basic Personality Research

Lastly, major advances in our understanding of the structure of adult personality as embodied in the 5 factor model--Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness--have led to gains in our understanding of health perceptions, coronary prone behavior and creativity.

Personality Influences on Women's Health Perceptions

Understanding the factors which determine perceptions of health and symptom reports is particularly important in dealing with aging persons who are likely to be facing new and increased medical problems over time. Our previous research has underscored the importance of distinguishing medical and psychological determinants of symptom reporting. The complaints individuals make reflect not only their medical condition, but also their evaluation of it, which is systematically influenced by the personality disposition of neuroticism. Previous studies from this Laboratory have shown that the personality dimension of neuroticism leads to exaggerated medical complaints in men; new results reported this year demonstrate that neuroticism is related to health perceptions in women also. The popular conception that older women, in particular, are hypochondriacs is incorrect; unfounded medical complaints do not increase with age.

Clarifying Coronary-Prone Behavior

The failure of global type A to predict coronary disease in several recent studies has focused attention on specific components that may be implicated in the etiology of CAD; of these Potential for Hostility has shown the greatest promise. Research in collaboration with Professor Theodore Dembroski of UMBC and other investigators has shown that Potential for Hostility is related to the willingness to express but not the tendency to experience anger. This finding is consistent with the hypothesis that the toxic component of type A may be related to the broad personality dimension of Agreeableness vs. Antagonism.

Personality Predictors of Creativity

For the past 35 years, researchers have worked to identify predictors of creativity. In the area of personality, a number of traits have been found to characterize more creative individuals, including tolerance of ambiguity, breadth of interest, and aesthetic interests. Research done by Laboratory scientists has shown that most of these traits can be understood as aspects of the larger personality dimension of Openness to Experience. A study of men in the BLSA demonstrated that more open individuals scored higher on divergent thinking tests and scales specifically developed to measure creative potential. Understanding its psychological bases may help in designing interventions to facilitate creativity across the lifespan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00180-01 LPC
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Stress, Coping and Personality in Aging Men and Women		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Paul T. Costa, Jr., Chief, Personality Stress and Coping Section, LPC, GRC, NIA Robert R. McCrae, Research Psychologist, PSC, LPC, GRC, NIA Alan B. Zonderman, Senior Staff Fellow, PSC, LPC, GRC, NIA Catherine M. Busch, Staff Fellow, PSC, LPC, GRC, NIA Theodore M. Dembroski, Guest Worker, PSC, LPC, GRC, NIA William E. Whitehead, Guest Worker, FSKMC		
COOPERATING UNITS (if any) Department of Psychiatry, Duke University Medical School Epidemiology, Demography, and Biometry Program, NIA National Center for Health Statistics		
LAB/BRANCH Laboratory of Personality and Cognition		
SECTION Personality, Stress and Coping		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Md 21224		
TOTAL MAN-YEARS 5.4	PROFESSIONAL 4.9	OTHER 0.5
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input checked="" type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <p> This project is concerned with the effects of stressors, coping mechanisms, and enduring personality dispositions on psychological and health outcomes. One study examined the course of psychological well-being in a nine-year followup of a national survey, and found no change in mean levels attributable to aging; further, individual differences in well-being were equally stable for men and women who had and had not experienced changes in marital or employment status or state of residence. A second study used data from the Baltimore Longitudinal Study of Aging (BLSA) to examine age differences and changes in divergent thinking ability, and showed consistent but modest declines after age 40. In a related study, divergent thinking ability was shown to be related to the personality disposition of Openness to Experience, suggesting that Openness may be an element in the prediction of creativity. A retrospective study of the childhood antecedents of adult personality showed a limited role for parent-child relations. An analysis of anger and hostility in college-age and adult samples showed that the expression--but not the experience--of anger is related to Potential for Hostility and Anger In, which have been shown to predict CHD. Studies of hypertension and personality in BLSA men and women showed that neuroticism is related to somatic complaints, and is in fact a stronger predictor of self-reported health than is hypertensive status. This project combines Z01 AG 00075-07 LBS and Z01 AG 00076-06 LBS. </p>		
IRP-LPC-519		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 AG 00062-13 LPC
PERIOD COVERED October 1, 1985 to September 30, 1986		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Daydreaming and Aging: Normative and Experimental		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)		
PI:	L. M. Giambra, Ph.D.	Senior Investigator LPC, GRC, NIA
	R. E. Quilter, BSEE	Electronics Tech. LBS, GRC, NIA
COOPERATING UNITS (if any)		
Laboratory of Behavioral Sciences		
LAB/BRANCH Laboratory of Personality and Cognition		
SECTION Cognition Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, MD 21224		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.8	.7	.1
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) One purpose of this work is to determine the parameters of <u>task-unrelated-thought intrusions</u> , TUTs, (<u>daydreaming/mindwandering</u>) as well as related mental activity such as <u>insight</u> and <u>concentration</u> . A second purpose is to investigate the relation between <u>sustained attention</u> and age. The purposes are accomplished through the use of controlled laboratory studies and retrospective questionnaires. Outcomes derived from these purposes and obtained during the reporting year were: (a) age was found to affect the magnitude of the effortful component of the vigilance decrement function with the young and the elderly having similar decay rates and both having larger decay rates than middle-aged; (b) the frequency of TUTs in 6.6 hours recording during 12 vigilance tasks was found to be strongly and inversely related to age; individuals over 60 years old had 83% fewer TUTs than 17-29 year olds; (c) arousal during vigilance was found to be unrelated to level of extraversion as predicted by one personality theory; (d) men using strategies with aggressive and deliberate involvement in the vigilance task detected more targets than men using passive involvement and concentration strategies. Efforts over the next fiscal year will include an analysis of: (a) 7-10 year longitudinal changes in retrospectively reported daydreaming characteristics, (b) relationships between aspects of sexual activity in women and their level of sexual daydreaming, (c) the time course of TUTs during vigilance, (d) the relation of TUT frequency during vigilance to general retrospective reports of daydreaming, (e) the relation between the attentional demands of a vigilance task and the frequency of TUTs, (f) the relation between success on memory tasks usually requiring "creative" thought generation for high level performance and the frequency of TUTs, and (g) the temporal stability of frequency of TUTs during a laboratory task.		
IRP-LPC-536		

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-25 LPC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Problem Solving and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator; Name, title, laboratory, and institute affiliation.)

PI: D. Arenberg

Section Chief

LPC, NIA

Others: L. M. Giambra
J. D. Sinnott

Senior Investigator

LPC, NIA

Towson State University

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

1.0

PROFESSIONAL

.3

OTHER

.7

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Among the goals of this project are to describe age differences and changes in reasoning performance and to investigate psychological processes underlying such age-related performance. Data collection continues for the longitudinal study of concept problem solving of men and women. Cross-sectional analyses of the women's concept-problem-solving performance produced results quite similar to those for the men. The mean number of problems solved correctly declined monotonically from the twenties to the eighties, and the correlation with age was $-.43$. Measures of effectiveness for three types of problems were also correlated with age. The correlation between age and effectiveness on complex problems with low initial information was $-.73$, the highest age correlation ever found for cognitive performance in the Baltimore Longitudinal Study of Aging.

IRP-LPC-541

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00065-26 LPC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Verbal Learning and Age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation.)

PI: D. Arenberg

Section Chief

LPC, NIA

Others: L. M. Giambra
J. D. Sinnott
E. A. Robertson-TchaboSenior Investigator
LPC, NIA
Towson State University
University of Maryland,
College Park

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

PROFESSIONAL

OTHER

2.0

.5

1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Among the goals of this project are to describe adult age differences and changes in memory and learning performance and to investigate psychological processes underlying such age-related performance. This year an extensive longitudinal analysis of individual regression measures of change in vocabulary was carried out. It is generally accepted in gerontology that an individual's world knowledge does not decline with age. One of the ways such knowledge has been measured is with vocabulary tests. Longitudinal analysis of 12-year (3 points) and 18-year (4 points) changes in WAIS Vocabulary performance of the men in the Baltimore Longitudinal Study indicates small mean declines for the group who were in their sixties and seventies when measured initially. These declines together with the small mean increases for the young groups produced a correlation of $-.42$ between age and change in vocabulary.

IRP-LPC-544

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00066-25 LPC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Perceptual Retention and Age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	D. Arenberg	Section Chief	LPC, NIA
	E. A. Robertson-Tchabo	University of Maryland, College Park	
	J. D. Tobin	Chief, Applied Physiology Section	LCP, NIA

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

1.1

PROFESSIONAL

.4

OTHER

.7

CHECK APPROPRIATE BOXES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project is to describe adult age differences and age changes in nonverbal memory performance. Nonverbal memory is measured in the Baltimore Longitudinal Study of Aging (BSLA) with the Benton Visual Retention Test (BVRT). Previous analyses of six-year and twelve-year longitudinal data indicated that for men, performance on the BVRT declines late in life. This year, extensive analyses of individual regression measures of change found substantial mean declines in the groups of men who were in their sixties or seventies when first tested. The correlation of age with change was $-.38$. These regression measures of change were based on 12 years (3 points) or 18 years (4 points) of longitudinal data.

Also this year, the BVRT was one of the measures included in a comparison of noninsulin dependent diabetic men with healthy age-matched men. There is some controversy in the literature about the effects of diabetes on cognitive performance; all of those studies were cross-sectional. No differences were found in the cross-sectional analysis or the longitudinal comparisons of change in BVRT performance in the BLSA. No support was found for the hypothesis that diabetes accelerates age declines in cognitive performance.

IRP-LPC-548

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00080-C1 LPC

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects On Automatic and Effortful Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D.

Senior Investigator LPC, GRC, NIA

COOPERATING UNITS (if any)

Department of Psychology, University of South Carolina, Columbia, South Carolina
(A. D. Fisk).

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS

.1

PROFESSIONAL

.1

OTHER

0.0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This work's purpose is to examine aging's influence upon the development and enactment of automatic and effortful informational/attentional cognitive processes. This purpose is accomplished through controlled laboratory studies. A study investigating the development of automatic visual detection of representatives of semantic categories was carried out on 7 young, 7 middle-aged, and 5 elderly subjects. The task was visual search in which one to three semantic categories were first memorized and searched for in a series of two word visual displays. Automatic detection was defined as having occurred when the time for detection was equal regardless of the number of categories memorized. All subjects underwent 4200 training trials with the result that all young and middle-aged subjects developed automatic detection, 64 to 69 years old showed "partial" automatized detection, and the three subjects 71 to 88 years did not show any automatized detection of memorized categories. The 71-88 year olds received an additional 2100 training trials and still did not show any evidence of automatization.

It now remains to explain the loss of the automatization process in visual detection in 70+ year old individuals. To this end three additional experiments will be carried out. The first will present 70+ year olds with a very simple visual search task which will involve a search for numbers and an alphabetic letter or two letters. It is expected that automatization of detection will occur here and hence demonstrate that 70+ year olds can achieve it. The second study will investigate different methods of training. The third study will investigate the extent to which previously learned automatic processes, arithmetic addition and multiplication, have been retained.

This project's significance lies in describing and explaining maturational changes in the development of automatic visual detection which is so important in our daily lives.

IRP-LPC-551

Room Library, Building 10
National Institutes of Health
Bethesda, Md. 20892



<http://nihlibrary.nih.gov>

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

AUG 1987





3 1496 00324 8393